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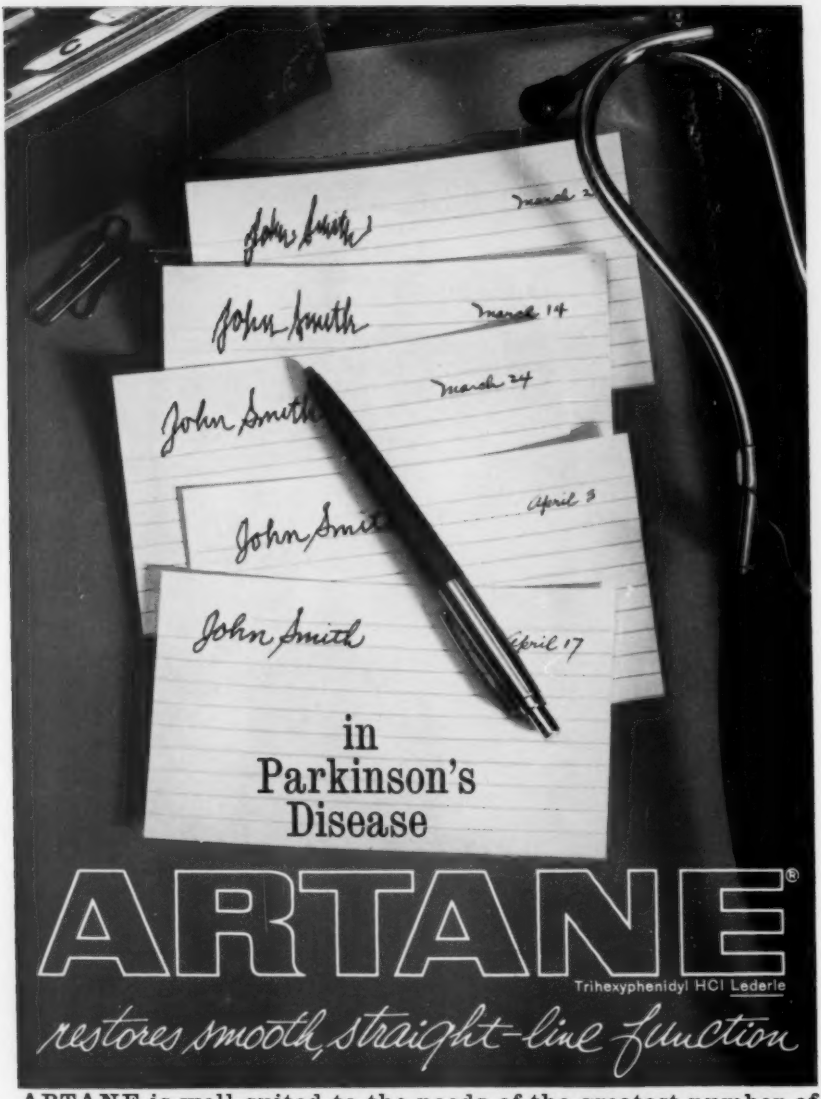

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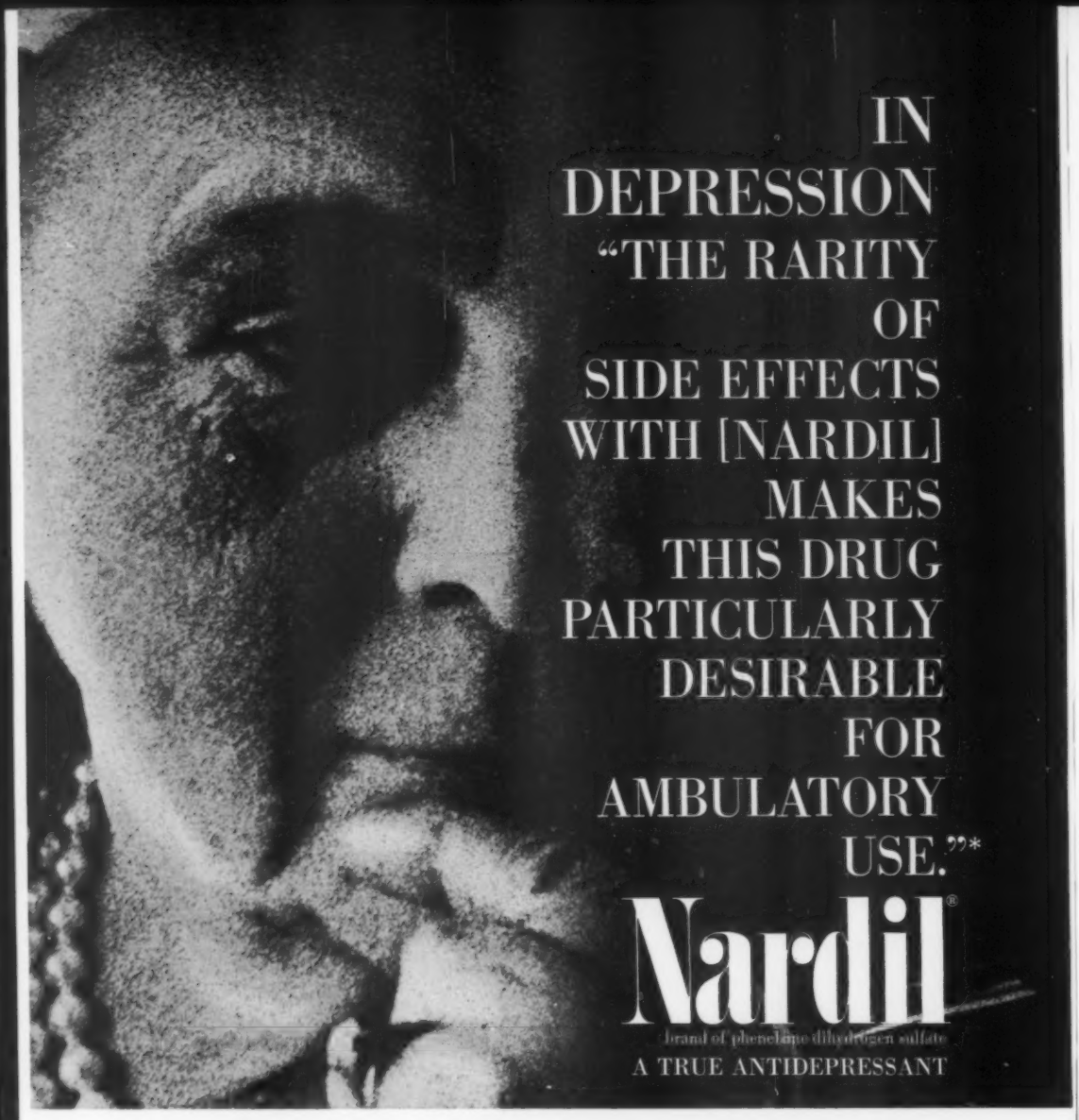
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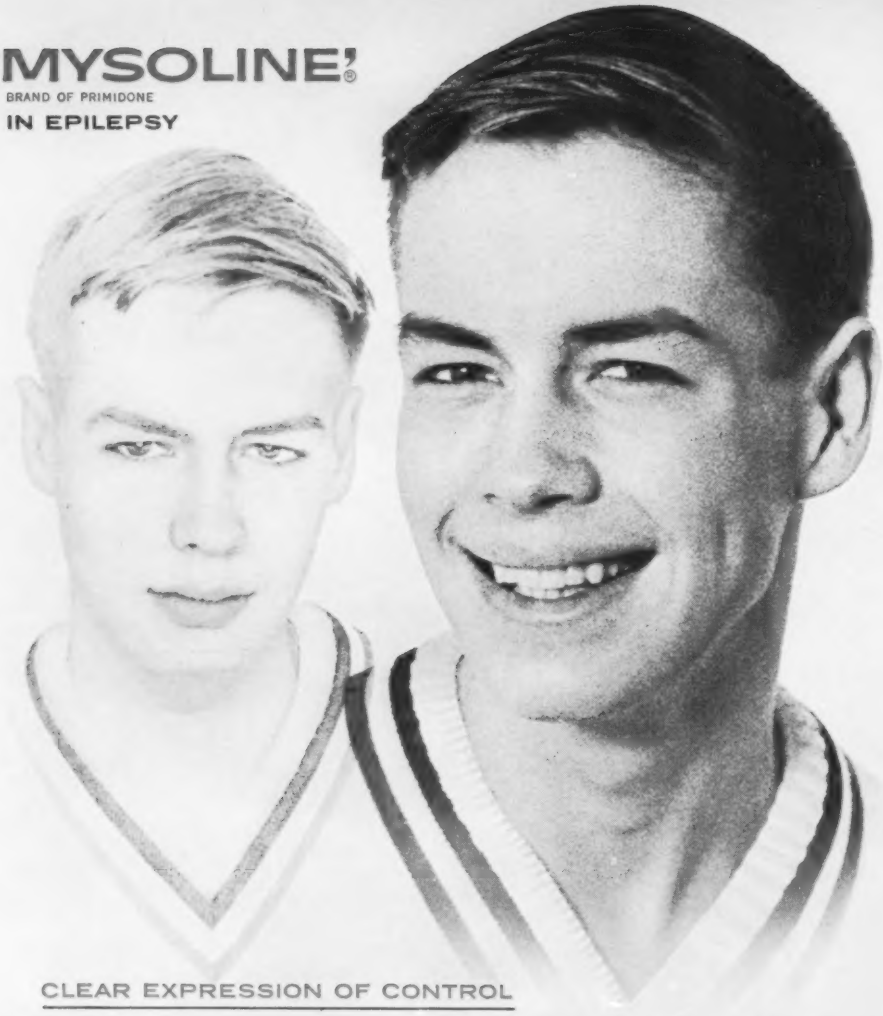

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Neurology Volume 11 • Number 5

Toxoplasmic polymyositis

Lewis P. Rowland, M.D., and Melvin Greer, M.D.

In 1939, Wolf, Cowen, and Paige[1] demonstrated that a form of congenital encephalomyelitis is due to Toxoplasma gondii. The infection, inapparent in the mother, is presumably transmitted to the fetus in utero.

Since the original description, a variety of acquired forms of the disease has been described. The infection may be asymptomatic, as indicated by the widespread distribution of antibodies in the general population, more than 25% in some areas.[2]

Symptomatic acquired disease has been discussed in several recent reviews.[2–4] The most commonly recognized form is manifest by fever, rash, and adenopathy. In some cases, there is evidence of myocarditis or pneumonitis. The illness is usually self-limited, but convalescence may be prolonged for several months. Acute encephalomyelitis may be fatal.[5–11] It has been estimated that about 7% of all cases of "glandular fever" and 5% of all cases of adenitis of unknown cause are due to toxoplasmosis. Some cases of acquired chorioretinitis are also associated with toxoplasma infection, but the frequency has not been ascertained.[2] Delineation among these several syndromes is not precise because clinical manifestations in an individual case may include features from more than one category.

In postmortem examination in fatal cases, the organism has been found in the brain, lungs, and heart. The muscles have not been described in most autopsy reports, but the parasite was found in skeletal muscle in 2 cases,[6,12] and in only 1 case of fatal disseminated infection were the muscles specifically stated to be normal.[9] Histologic evidence of polymyositis, muscle necrosis, and an inflammatory cellular reaction was present in those cases in which the organism was demonstrated in muscle.

In addition, the organism has been found in muscle biopsy of living patients on several occasions,[6,12–16] and, because lesions were seen in 4 of 14 cases they reviewed, Calahan, Russell, and Smith[17] suggested that muscle biopsy might be a useful diagnostic tool in suspected cases. In 1 case, the diagnosis was actually first suspected when the parasite was identified in a muscle biopsy specimen.[6] This was true in another case,[18] but doubt has been cast upon the validity of the diagnosis because the results of animal innoculation were not characteristic and serologic tests were negative.[6] Jacobs and Melton[19] demonstrated muscular dissemination of organisms in experimental infection of rats and found that the toxoplasma might be irregularly distributed in a single muscle. Therefore, as has been true in some human cases,[20] a normal muscle biopsy would not necessarily exclude involve-

From the Department of Neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, Presbyterian Hospital, New York City.

Dr. Rowland is a Scholar of the Sister Elizabeth Kenny Foundation.

Dr. Greer was supported in part in this work by Special Clinical Traineeship BT-319 Cl from the National Institute of Neurological Diseases and Blindness.

ment of this tissue. Demonstration or isolation of the organism by muscle biopsy would not necessarily establish the presence of an acute infection, since the parasite may persist for months after infection.

Despite the histologic evidence, clinical symptoms due to polymyositis have not been clearly described in any previous report. The chronic fatigue which retards the convalescence of patients recovering from acute infection has been attributed to muscular lesions.[2] Muscular aches and pains have been noted in several cases.[15,20–22] Weakness, lassitude, or fatigue is mentioned in the histories of several patients,[5–10,20,21,23–25] but, without further description, these terms do not permit evaluation of muscular function. Except when specifically stated to be normal,[8,14] no mention of strength is provided in reports of the actual examination of these patients. In only 1 case[15] was weakness documented in any way; there was no weakness during the acute illness, but, after defervescence, "ambulation . . . progressed slowly because of weakness and pain in the legs . . ." Even in this instance, evaluation of muscular function is difficult because the authors attributed the prolonged disability to emotional factors. In 1 other case,[7] weakness may have been a significant symptom, but the patient was not examined during this phase of the illness.

In the following case, symptoms of polymyositis dominated other manifestations of the infection.

CASE REPORT

B. L. (P.H. No. 143-14-26), a 33-year-old truck driver, became ill at the end of May 1959. He had fever (100 to 102° F.), diffuse muscular aches, weakness of the arms and legs, and stiffness of the neck and back. These symptoms progressed, and, during the second week, he had difficulty in walking, climbing stairs, and raising his arms to shave. Occasionally, he felt spontaneous twitching of the muscles. He also noted a tender swelling of the right side of his neck. He was treated with cortisone, 100 mg. orally each day for four days. This was without effect, and, one week later, on June 22, 1959, he was referred to Presbyterian Hospital. He had had some pain on swallowing and had lost 10 lb., but there had been no rash or pulmonary or visual symptoms. He had not been overtly exposed to any unusual source of infection. The past history and systemic review were otherwise unremarkable.

Examination. The patient's temperature was 101° F., and he appeared acutely ill. He kept his spine rigid when standing or walking, and the paraspinal muscles were tender. He was unable to sit for prolonged periods because of pain in the back. He complained of pain in the neck when it was passively flexed, but there was no nuchal rigidity and neither Kernig nor Brudzinski signs were elicited. Generalized enlargement and tenderness of the lymph nodes were noted. The pharynx showed scattered petechiae and was erythematous, but there were no skin lesions. The liver was slightly tender, and its smooth edge was felt about 2 cm. beneath the costal margin. The spleen was not felt; heart and lungs were normal.

The patient was lucid, and the cranial nerve functions were all normal. His gait was slow and shuffling; he was unable to lift his thighs and had difficulty in walking on toes or heels. He could not rise from a squatting position nor climb onto a chair. The muscles of the pelvic girdle showed weakness, more marked on the right, against slight resistance; slightly less severe but symmetric weakness of shoulder and neck muscles was found. Strength was less impaired in distal muscles. Diffuse muscular tenderness was noted, but no abnormalities were found on palpation of the muscles, and there was no muscular wasting or twitching. The quadriceps and Achilles reflexes were depressed in the right leg only. Deep reflexes were normal in the arms, as were abdominal and plantar reflexes. Sensation was normal.

Laboratory data. The following were normal: blood sugar, urea nitrogen, calcium, phosphorus, sodium, potassium, chlorides, proteins (electrophoresis), bilirubin, sulfobromophthalein excretion, cephalin flocculation, alkaline phosphatase, protein-bound iodine; white blood cell count (5,400) and differential; lupus erythematosus cell preparations and agglutination tests; Latex fixation, antistreptolysin, and C-reactive protein studies; serologic tests for syphilis, typhoid, paratyphoid, brucella, infectious mononucleosis (heterophile), poliomyelitis, Coxsackie, and ECHO viruses; cultures of pharyngeal swab for adenovirus, influenza, poliomyelitis, Coxsackie, ECHO, herpes simplex, and vaccinia virus and rickettsial pox; cultures of stool for poliomyelitis, Coxsackie, and ECHO viruses; Trichinosis skin test; examination of urine for urobilinogen, porphobilinogen, and bile; electrocardiogram; roentgenogram of chest; cerebrospinal fluid pressure, protein, sugar, cell count, Kolmer, and gamma globulin; Coomb's test.

Abnormalities were: [1] Hemoglobin was 13 gm. per cent on admission and fell progressively to 10.2 gm. per cent on June 29, when the red blood cell count was 3,520,000 per cubic millimeter and the reticulocyte count was 3.2%. [2] The erythrocyte sedimentation rate was 44 mm. in one hour on June 23 and 60 mm. on June 30. [3] Thymol turbidity was positive (3+) on June 24 but negative on June 29. [4] Urinary creatine excretion was 373 mg. in twenty-four hours and creatinine,

1,337 mg. [5] Electromyographic studies showed that motor units were of short duration, and there were complex units; hyperexcitability of muscle was indicated by showers of fibrillation potentials after voluntary contractions or manipulation of the needle and sporadic fibrillation potentials at rest. [6] Serum phosphohexose isomerase was 600 units on June 23 and 273 units on June 30 (normal, less than 40 units); corresponding values for lactic dehydrogenase were 1,860 and 1,070 (normal, less than 400 units), but cerebrospinal fluid enzyme activities were normal. [7] Tuberculin skin test was positive at dilution of 1:10,000. [8] Toxoplasmosis hemagglutinin titer, 1:512; precipitin titer positive (3+).

Course in hospital. During the first few days, there was little change and his temperature remained elevated. A biopsy of sternomastoid muscle and a cervical lymph node was done on June 26; the muscle appeared normal microscopically, but there was no recognizable lymph node in the specimen submitted. It was not thought to be necessary to repeat the node biopsy because there was considerable clinical improvement without specific therapy, and he was allowed to go home on June 30, after four days without fever.

Subsequent course. On the evening of June 30, after he arrived home, the patient noticed a rash on his back, buttocks, and arms and his temperature was 100° F. Two days later, he was seen at the hospital and had a macular rash over the back and buttocks; however, he was afebrile, and the dermatitis disappeared within a day or two. He gradually improved, and serum enzymes were normal on July 17, but there was still slight weakness and adenopathy in August. He did not feel well enough to return to work until September.

Due to unfortunate circumstances, it was not until February 1960 that we learned the results of serologic studies for toxoplasmosis which had been made during the acute illness. The patient was contacted once again. He was asymptomatic, and examination was entirely normal. He had no adenopathy, hepatomegaly, weakness, reflex asymmetry, or chorioretinitis.

On February 9, 1960, the toxoplasmosis hemagglutination titer was 1:8,192, the precipitin test was 2+ positive, and the dye test was positive at a dilution of 1:1,024. The skin test for toxoplasmosis was also positive. In the light of these findings, the original sections of the muscle biopsy were reexamined by Drs. Abner Wolf and David Cowen but no organisms were seen. Serum protein electrophoresis, hemoglobin, red and white blood cell counts, erythrocyte sedimentation rate, and lactic dehydrogenase were all normal. Serologic tests for leptospirosis and brucellosis were normal. A Kveim skin test for sarcoid and electromyograms were normal. Subsequent serologic studies are included in the table.

DISCUSSION

The diagnosis of toxoplasmic infection in this case rests upon serologic evidence—not only the significantly high titers of the hemagglutination and dye tests, but the rise and fall in antibody titer indicated by the hemagglutination test (see table). The diagnosis is supported by the positive skin test, although this only indicates infection some time in the past. Taken as a group, these tests provide reasonably reliable proof that the acute episode was, in fact, due to this organism, even though the parasite was not actually demonstrated.[3,4,26] Because of the long intervals between tests, probably the peak antibody titers were missed.

The only alternative explanation requires 3 circumstances: [1] the original hemagglutination titer was due to an asymptomatic toxoplasmic infection some time in the past; [2] the subsequent rise in titer was due to reexposure to toxoplasma during the seven-month interval between the febrile illness and the second serologic test; and [3] the symptoms described, although similar in nature and duration to those of previously reported cases of toxoplasmosis, were not due to this organism (nor to any of the long list of other possible etiologies, studies for which were negative). This is possible but seems unlikely.

SEROLOGIC DATA* IN CASE OF PRESUMED TOXOPLASMIC POLYMYOSITIS
(ONSET OF SYMPTOMS — May 31, 1959)

Date	*Skin test*	*Precipitin test*	*Hemagglutinin titer*	*Dye titer*
June 24, 1959	Not done	3+	1:512	Not done
February 9, 1960	+	2+	1:8,192	1:1,024
May 10	+	Negative	1:512	1:256
August 19	+	Negative	1:512	1:64

*The precipitin test and the hemagglutination tests for antibodies to Toxoplasma gondii were performed in the laboratory of Dr. G. R. O'Connor (Department of Ophthalmology, Columbia University). Modifications of the original methods[27,28] will be described in a forthcoming monograph by Dr. D. Khorazo. The dye test[29] was done at the U.S.P.H.S. Communicable Disease Center, Chamblee, Ga.

The diagnosis of polymyositis was based primarily upon the clinical picture and was supported by electromyograms, creatinuria, and abnormal elevation of serum enzymes. (The enzymatic abnormality is sometimes present with liver disease, and this may have been a factor here, in view of the hepatomegaly and positive thymol turbidity test. However, all other liver function tests were normal, and the serum enzymes remained elevated after the thymol turbidity had returned to normal.) Because the muscle biopsy was normal, it might be more accurate to use the less precise word, "myopathy," to describe this disorder, but, since inflammatory lesions may have been present elsewhere in the same or other muscles and since we have presumed an infective etiology, "polymyositis" seems a reasonable appelation. This is in keeping with the histologic lesions reported in other cases, as discussed above.

Interest in and recognition of cases of both acquired toxoplasmosis and polymyositis have been increasing, but in a sense these studies are following different paths. With toxoplasmosis, a single agent causes a variety of different syndromes. Polymyositis, a clinical syndrome characterized fundamentally by proximal muscle weakness, is being shown to be due to or associated with a variety of different causes.

Recognition of toxoplasmic polymyositis is of more than academic interest; the diagnosis hopefully implies a usually self-limited course, and, for more severe or more protracted cases, treatment with pyrimethamine may be of value.[3,4,14,22]

SUMMARY

A case is described in which clinical features of subacute polymyositis were attended by fever and adenopathy. On the basis of skin sensitivity and serologic tests, it has been deduced that the clinical disorder was caused by Toxoplasma gondii.

The authors are indebted to Dr. L. Jacobs, National Institutes of Health, for advice in evaluating the serologic data. Viral studies were performed in the Laboratories of the New York City Board of Health.

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Factors related to recording photic potentials from cat cerebellum

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In a previous communication from this laboratory,[1] the importance of considering the pharmacologic state in recording optic potentials from the cerebellum was studied. The present experiments were designed to study the possible field effects (current spread) of optically active portions of the cerebrum on cerebellar recordings. In addition, the interaction between alpha-chloralose and strychnine was investigated.

Materials and Methods

Operative procedure. Under light ether anesthesia, the dura was exposed covering Larsell's[2] areas VI and/or VIII and optically active areas of the cerebrum. The animal was oriented in a Lab-Tronics stereotaxic device and immobilized by 2- to 4-mg. doses of Flaxedil by polyethylene catheter in the femoral vein. Artificial respiration was supplied by tracheal cannula. After an interval of an hour or more, the dura was opened, electrodes were placed, and recording was begun.

Electrodes. The smallest were made from .0159-in. diameter pulled Nichrome wire cut to appropriate lengths, electrolytically pointed by the method of Grundfest, Sengstaken, and Oettinger,[3] insulated with clear baking varnish, and heat-treated until the varnish retracted, exposing tips of 2 to 10 μ.

Larger electrodes were produced from prepointed .017-in. diameter Staybrite wires, factory cut to 4-in. lengths, insulated, baked, and lightly rubbed on fine ground glass to expose tips of 50 to 150 μ. Pairs of the above 2 types were bound together after insulation to form bipolar electrodes having interelectrode tip distances of from 100 to 1,000 μ.

Silver ball electrodes were employed for surface recording, the exposed surfaces being about 500 μ in diameter, separated by distances varying from 400 μ to about 1,000 μ.

For comparison of electrode types, tetrapolar electrodes were used, consisting of a bipolar microelectrode and a bipolar silver ball electrode. The components were arranged in line, either with the microelectrodes first or with the microelectrodes between the silver balls. A switch box was employed to allow any 2 of the 4 leads to be used together.

The placement of the electrodes varied from experiment to experiment, as described in Results below. Action potentials were passed through cathode-loaded input stages, amplified through Grass P_6 preamplifiers, visualized by DuMont 322-A or 333 oscilloscopes, and photographed with Grass C4F cameras. Amplifiers were adjusted to permit a high degree of differential action (common signal rejection;) external shielding was used when needed.

Stimulation. Photic stimulation was carried out as described in an earlier paper[1] using a Grass PS-2 photic stimulator triggered at a controllable point by a Grass S-4 stimulator. The parabolic reflector of the strobe lamp was placed 10 to 12 in. from the left cornea and covered by a cone-shaped shield, the open apex of which was placed close to the cornea to avoid stimulation of the contralateral eye. The light flash duration was approximately

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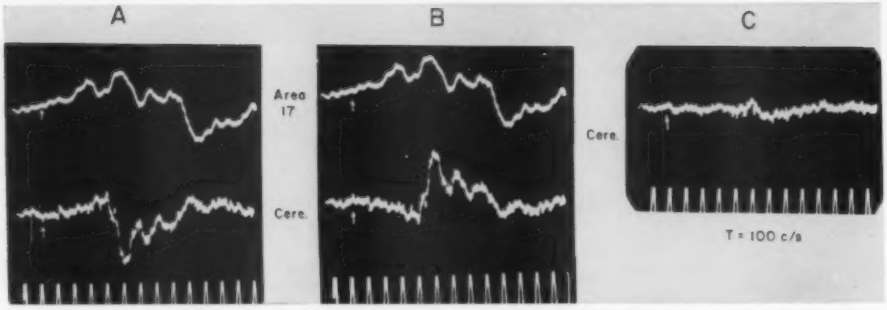

Fig. 1. Effect of optically active areas outside cerebellum. [A] Top trace, area 17 record taken with bipolar microelectrodes. Lower trace, monopolar microelectrode record with different on cerebellar cortex and indifferent on bone overlying area 17. [B] Top trace, as in A. Bottom trace, with same electrode placement as in A but leads reversed. [C] Bipolar microelectrode recording from cerebellar cortex. Time line, 100 cps

10 μsec. and 7.5×10^5 candle power—a very brief, very intense stimulus.

Types of experiments. The experiments carried out on 40 cats can be divided into 3 types: [A] effect of optically active areas outside cerebellum upon cerebellar recording, [B] comparison of electrode types, and [C] pharmacologic studies.

[A and B] In the first and second group, recordings were carried out with bipolar and monopolar needle electrodes as well as silver ball electrodes. With a bipolar electrode in an optically active area of the cerebellum for control recordings and using only one-half of the bipolar, either a monopolar needle electrode or silver ball as the indifferent electrode was placed in varying positions through a 180° arc oriented in an anterior-posterior fashion around the different electrode. Recordings were taken before and after administration of 50 mg. of alpha-chloralose per kilogram. Simultaneous recordings were taken from other optically active portions of the brain for comparison with the wave forms and delay of the cerebellar recordings.

[C] In the third type, the effects of strychnine and chloralose were tested in relation to their ability to induce or modify cerebellar and other photic responses.

RESULTS

Effect of optically active areas outside cerebellum upon cerebellar cortical recording. Figure 1 shows recordings taken from area 17 by bipolar electrodes (top trace) and monopolar recordings taken from cerebellar cortex with an indifferent electrode located on the bone near area 17 recording site.

Figure 1A (bottom trace) shows typical cerebellar response presumably recorded from the different electrode on the cerebellar cortex.

Figure 1B shows response after the electrode leads had been switched, making the indifferent the different electrode. Note the correspondence of the 3 waves of the cerebellar response with the second, third, and fourth waves of the response from area 17. The first wave of the area 17 response has no correspondence in the cerebellar pattern.

Figure 1C, a bipolar recording of the cerebellar response to photic stimulation, is shown taken from the same area of the same animal as that shown in Figure 1A and B. The bipolar recording shows a very small or questionable response.

In Figure 2, cerebellar responses are shown recorded from a central different needle electrode and a roving silver ball electrode placed at various positions around it before and after chloralose. In the first column, before the administration of chloralose, cerebellar cortical responses are found only when the indifferent electrode is located on parietal bone over area 17. The bottom trace in each of the 5 recordings shows the response of the superior colliculus as recorded by a bipolar electrode for use as a check on the continuing activity of the optic system.

In the second column, responses are recorded showing the "Activation effect" of intravenous alpha-chloralose. The top trace in each of the 4 pairs of recordings shows cerebellar cortical response. It will be noted that the response is greatest in amplitude when the indifferent electrode is located near area 17 and that the amplitude progressively decreases as the indifferent is moved caudally to a position just lateral to the different electrode. Positioning the indifferent caudal to the different electrode in the nuchal musculature produces a reversal in polarity of the response from positive to negative.

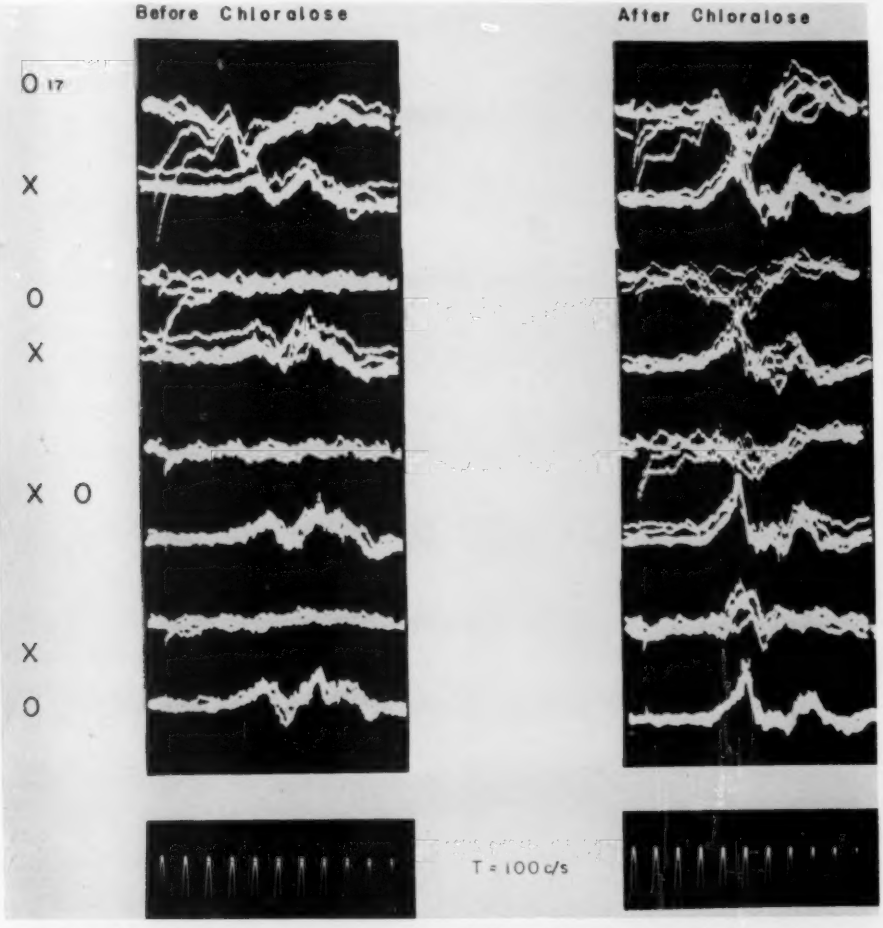

Fig. 2. Effect of optically active areas outside cerebellum; 5-time repeat records of responses to photic stimulus before and after intravenous administration of chloralose. Top trace of each pair of records was made, using as the different a monopolar microelectrode (X) on cerebellar cortex and as the indifferent, a roving monopolar silver ball electrode (O). Relation between different and indifferent is indicated on left by placement of X and O. Bottom trace in all pairs is a bipolar microelectrode record from superior colliculus. Time line, 100 cps

It is interesting to note that the delay time of the so-called cerebellar response in this type of experiment is equal to that shown by the collicular response.

Comparison of electrode types. The use of closely spaced bipolar silver ball recording electrodes on the cerebellar cortex is illustrated in Figure 3. As shown, they recorded a response that may be lacking or extremely small when observed with bipolar microelectrodes. Further, responses that only appeared sporadically when observed with microelectrodes were shown to be constant when silver ball electrodes were used. The top traces of Figure 3 show 2 series of 3 consecutive records from the same cerebellum, after chloralose, using the same stimulus intensity. The time difference between each picture of each series was forty seconds, which tended to eliminate extinction. While only 1 of the responses recorded with microelectrodes was of good size and 1 response was missing entirely, large responses were seen in all records made with silver ball electrodes. In all cases, the bottom trace is a bipolar microelectrode record of area 17.

Because of the sporadic nature of the microelectrode pickup, graded responses to graded stimulus increase could not be recorded with this setup. The highest intensity of the graded stimulus series was 1,500,000 candle power, 16 times that of the lowest. Records taken with silver ball pickup electrodes from the cerebellar cortex permitted graded responses to be recorded as per Figure 4. While each increase of stimulus was double the preceding, the responses did not increase correspondingly, or even step-wise. The bottom trace in each pair is a bipolar microelectrode record taken from area 17.

Effect of chloralose and strychnine on cell populations of cerebellar cortex and superior colliculus and fiber components of optic chiasm. In animals immobilized with Flaxedil, 2 series of experiments were carried out. In the first series (Fig. 6), 50 mg. of alpha-chloralose per kilogram was administered intravenously and, after a delay of at least an hour, was followed by repeated intravenous injections of very small amounts of strychnine sulfate. In the second series (Fig. 5), the process was reversed, strychnine being injected

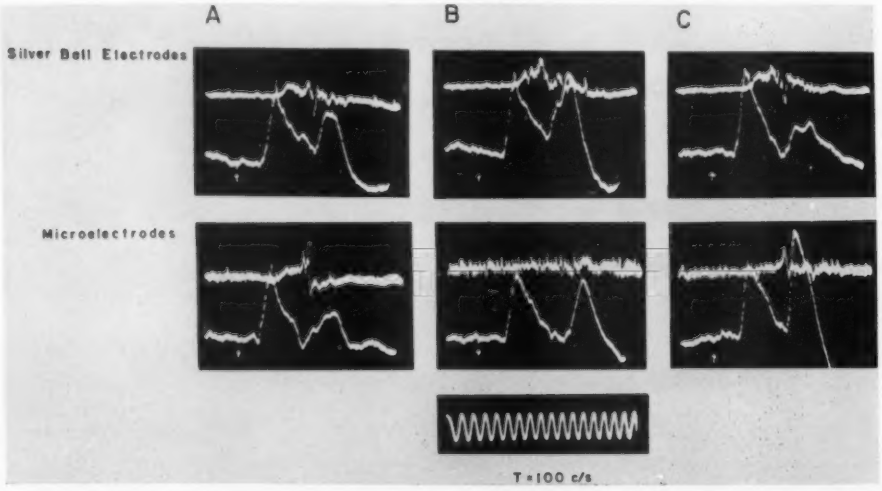

Fig. 3. Top traces of upper series are records of response to photic stimulus picked up by bipolar silver ball electrodes from cerebellar cortex by bipolar microelectrodes. Bottom traces in both series are bipolar microelectrode records of area 17 responses. Time interval between A and B and C of each series was forty seconds.

first, followed by administration of chloralose.

As shown in Figure 6, the effect of chloralose on cerebellar cortex and superior colliculus followed the pattern previously described,[1] producing a positive cerebellar wave and a decrease in the random spiking of cortical components. The addition of strychnine resulted in a large augmentation in amplitude and increase in complexity of form of the cerebellar wave. The colliculus response, complicated in its initial form, was not further complicated but was augmented in amplitude, showing the same decrease in spontaneous activity demonstrated by the cerebellar cortex. Specific wave form of the superior colliculus shown in Figure 6 is dependent, at least in part, on the position of the recording electrode within the colliculus and is alterable either in number of spikes or their polarity by the addition of chloralose and/or strychnine.

As shown in Figure 5, the intravenous injection of strychnine increased the random spiking of the cerebellar cortex but did not appreciably increase the activity recorded from the optic chiasm. The cerebellar cortex very rapidly developed a complex of 3 negative waves which could be augmented by the addition of another small amount of strychnine. No apparent change in the initial photic response of the chiasm resulted from the addition of strychnine. The addition of chloralose to this preparation resulted in a remarkable series of changes, in both the chiasm and cerebellar cortex. The first obvious result was a dramatic decrease in the random spiking of the cerebellar cortex. The cerebellar cortical complex of 3 negative waves showed a reversal of potential of the first wave from negative to positive, reduction or elimination of the second negative wave, and no change in the

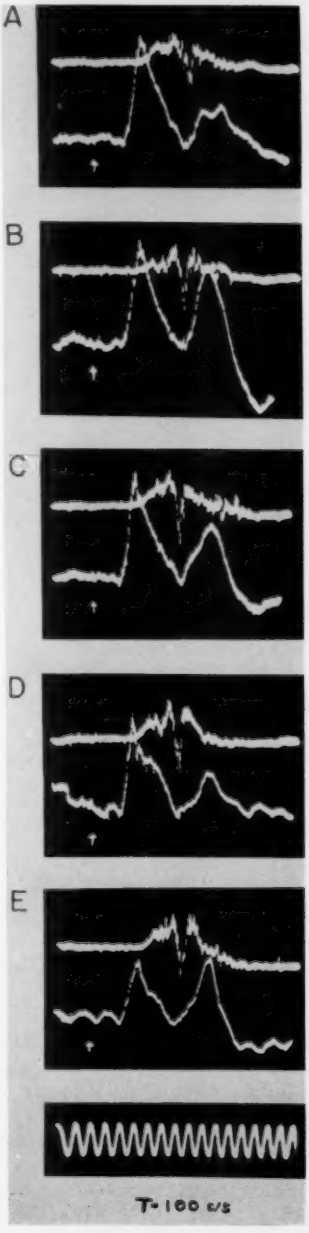

Fig. 4. Records of response to graded increase in photic stimulus. Stimulus intensity in candle power for each record: [A] 93,750; [B] 187,500; [C] 375,000; [D] 750,000; [E] 1,500,000. Stimulus duration in each case was 10 μsec. Top trace of each pair is response as recorded from cerebellar cortex by bipolar silver ball electrodes. Bottom trace is bipolar microelectrode record from area 17. Time line, 100 cps

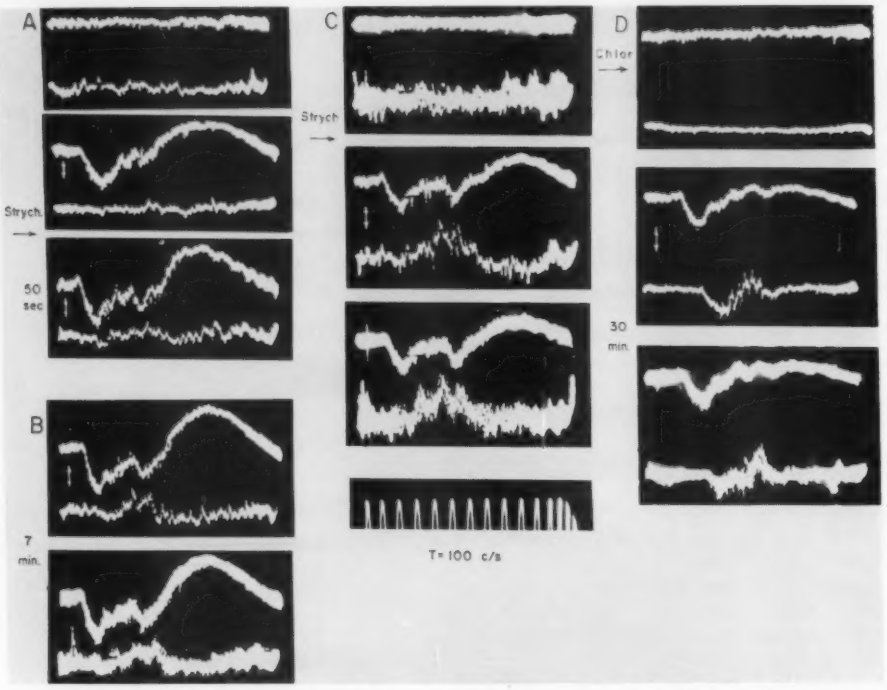

Fig. 5. Series of bipolar microelectrode recordings taken from optic chiasm (top trace) and cerebellar cortex (bottom trace). [A] First record is without stimulus, second with photic stimulus, third fifty seconds after administration of intravenous strychnine. [B] First record seven minutes after intravenous strychnine. Second record is a 5-time repeat. [C] First record a 5-time repeat without stimulus. Second, a single record after administration of additional strychnine, using photic stimulus. Third, a 5-time repeat. [D] First record after administration of chloralose but without stimulus. Second, with photic stimulus. Third, a 5-time repeat after interval of thirty minutes. Time line, 100 cps

third negative wave. An effect was also seen in the response from the fibers of the chiasm primarily concerned with a severe decrease in amplitude of the second positive wave.

DISCUSSION

Field effect problems. There have been numerous experimental reports to show the differences that exist in the response patterns obtained with electrodes of varying size and physical arrangement. This is especially true of recordings taken from the surface of the active area. Thus, a large series of recordings taken from various locations of surface of the spinal cord during dromic and antidromic stimulation of the dorsal and ventral root fibers differ greatly in their form, sign, and complexity, depending on the specific location of the electrodes relative to the active site. That this is true of the cerebral cortical areas and cerebellar cortical areas is evident on perusal of the literature.

The fact that size of the electrodes makes a difference in the kind and amount of electrical activity recorded is also well known. Large electrodes tend to be less discriminating than small or microelectrodes, recording large activity at a distance from the recording site rather easily. The position of the so-called "indifferent" electrode also exerts a decided

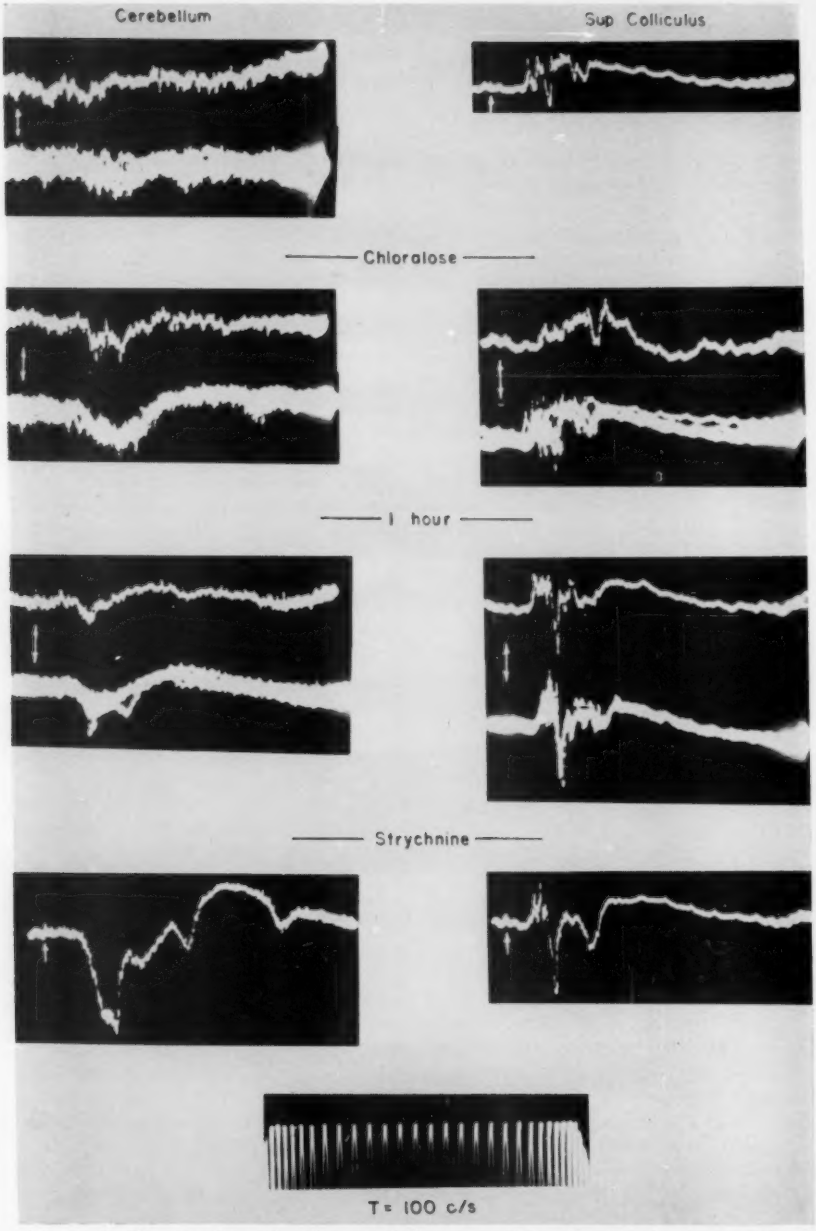

Fig. 6. Bipolar recordings taken from cerebellar cortex (left column) and superior colliculus (right column). Responses shown are recorded singly and in some cases are followed (lower trace in each set where applicable) by superimposition of 5 consecutive traces to establish reliability of single trace phenomenon. Top pair of traces in each column shows response to photic stimulation in Flaxedil-immobilized cat before intravenous administration of alpha-chloralose; next 2 pairs show increasing effect of alpha-chloralose over one hour. Last pair shows effect after intravenous administration of strychnine sulfate.

effect on the response recorded. It is usual to place the indifferent on bone or muscle at a distance from the site being investigated. It should be pointed out, however, that, while bone is ordinarily a neutral recording site for electrical activity when considered by itself, the material underlying the bone may be very active and consequently alter the neutrality of the indifferent electrode severely. Brazier[4] has reported that, in unanesthetized cats, the indifferent electrode could not be placed on the frontal sinus bone in experiments dealing with the photic response of the optic system, since the indifferent in this location records the electroretinogram. Similarly, the indifferent electrode located over or near optically active areas of the cerebral cortex in our experiments produced recordings which at the very least were affected by the activity of that cortex.

The use of pairs of electrodes the physical characteristics of which are not similar (for example, a microelectrode with a silver ball electrode as the indifferent) effectively unbalances the physical situation relative to the amplifiers and destroys the differential activity depended upon for discriminatory localization. It is unfortunate for the electrophysiologist that the optic system produces such large activity in so many locations, since this limits the number of places one can place an indifferent electrode and be assured of a neutral electrical position.

The position of the electrode pairs relative to the field of activity (the orientation of the electrodes relative to a longitudinal stream of activity, for example) must be considered when using large electrodes of similar type, particularly when the response pattern is fed into a differential preamplifier. When both electrodes "see" the same response to the same degree, that is, amplitude, the net result is the cancellation of the entire response, since each electrode sees the response in the phase opposite to that of its mate. The function of the differential amplifier is to eliminate material seen by both electrodes (for example, 60-cps activity). When one of the electrodes is more closely placed to the site of activity, it will record the response as the algebraic sum of the responses seen by both electrodes and the sign of the response will depend on the input lead pattern to the oscilloscope.

The response patterns recorded and illustrated in Figure 2 are examples of this type of activity. With the electrodes arranged longitudinally (anterocaudally), a response is recorded easily. As the indifferent is moved caudally, the response amplitude decreases, until, when the indifferent is located immediately lateral to the different electrode, the response pattern is no longer seen. The fact that the response is largest when the indifferent is located close to the cerebral optic area and decreases with movement away from this area indicates the true recording electrode was the indifferent, not the different. Small bipolar electrodes used under the same conditions in another animal show very little if any response in the cerebellar cortex, while large monopolars, with the indifferent located anterior to the different, demonstrate a large response.

An analysis of the delay times shown by the "cerebellar" recording compared to those taken from the superior colliculus (Figure 2) shows there is no apparent difference in delay, a fact that seems somewhat surprising considering their relative conduction distances. Either the conduction times to the cerebellar cortex and superior colliculus are the same (meaning there could be no possibility of the cerebellum receiving its incoming volley via the colliculus) or the cerebellar recording is spurious and must be referred information from a point outside the cerebellum via the indifferent electrode.

On the other hand, reference to Figure 1 and comparison of the response delay times obtained with small, closely placed, bipolar electrodes show a differential delay time, the superior colliculus showing the activity approximately 5 to 10 msec. before the time shown in the cerebellar cortex.

Comparison of pharmacologic agents. Strychnine in the presence of alpha-chloralose apparently cannot further radically change the action potential already obtained, except for augmentation of the response amplitude (Figure 6). An interesting change does occur when the situation is reversed, however. Chloralose, in the presence of strychnine, apparently has the property of abolishing one portion of the collicular response, changing the polarity of the first wave, and leaving the

third wave unchanged. The chiasmatic response, a fiber system response, is essentially unchanged, although the amplitude is decreased somewhat. It is interesting that the reversal of polarity occurs in a cell population area and recalls the experiments of Purpura, Girado, and Grundfest,[5] where the topical application of gamma-aminobutyric acid to the cerebral cortex resulted in changing the previously negative evoked potential to a positive one—a reversible change, the negative spike returning after the cortex was flushed with saline. We did not attempt to find such a reversal in our experiments because of the method of drug administration. Strychnine may produce its effect by hyperpolarizing the secondary neurons in a complicated system, producing 3 distinct spikes, while chloralose may act by hypopolarizing a certain number of neurons, leaving others less affected or untouched. The persistence of the third wave seems to indicate either a separate route, resistant to chloralose, from lateral geniculate to superior colliculus or a differential effect on the cells giving rise to fibers of varying diameter, allowing only the smaller, slower conducting fibers to react.

SUMMARY

1. With one electrode on the cerebellar cortex and a presumably indifferent electrode near an optically active area, photic responses will be recorded even though the cerebellar site may be inactive.

2. Large bipolar electrodes will record responses not recorded well, if at all, with bipolar microelectrodes.

3. Some effects of chloralose and strychnine on parts of the optic system have been discussed.

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Cerebrovascular disease

VIII. Role of nutritional factors

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ATHEROSCLEROSIS is known to have existed at least as early as 1500 B.C. because typical atherosclerotic lesions have been found in the aortas of Egyptian mummies.[1] However, it was not until 1856 that Virchow[2] described the fatty nature of the lesions of atherosclerosis, and, in 1904, Marchand[3] coined the term "atherosclerosis," taken from the Greek meaning, "hardened mush."

Following the experiments of Anitschkow and Chalatow[4] in 1913 in which they reproduced atherosclerotic lesions in rabbits by feeding them cholesterol, a great deal of interest developed in the nutritional aspects as playing a role in the pathogenesis of atherosclerosis. This development, of course, added support to the long-known fact that atherosclerosis tends to occur more frequently, prematurely, and severely in individuals suffering from diseases involving deranged lipid metabolism, such as familial xanthomatosis, diabetes, hypothyroidism, and lipoid nephrosis. However, although these observations have pointed to the relationship of atherosclerosis to endogenous errors of metabolism, they have done little to clear up the problem of nutrition and atherosclerosis other than indicating that the process is not exclusively diet-induced.

In spite of rapid advances in our knowledge of nutrition, very little information is available concerning the role of dietary factors in atherosclerosis and even less is known concerning cerebral atherosclerosis. Although the literature abounds with frequent inferences that nutritional factors may play a role in this degenerative process, it is generally agreed that there is no conclusive evidence that nutrition plays a direct role in atherosclerosis; in the vast majority of cases in man, there is no evidence of nutritional disturbances and no exogenous alteration of lipid metabolism.

Because of our inadequate knowledge of this subject, it was felt of value to investigate the possible role of nutritional factors to cerebral atherosclerosis in a consecutive series of 1,175 autopsies. In all these cases, the severity and extent of the atherosclerotic process was determined by using a simplified standard coding system[5–7] in which the degree of involvement of all arteries of the circle of Willis and their major branches was evaluated. A careful survey of the case history and the autopsy findings enabled us to select those nutritional factors that might be compared with the extent and severity of the cerebral atherosclerosis. We were able to select 4 possible areas dealing with a possible role of nutrition in the atherosclerotic process: [1] the nature of the histologic changes within the vessels; [2] the role of obesity; [3] the influence of malignancy; and [4] the role of diabetes.

NATURE OF THE DEGENERATIVE PROCESS

Most authors agree that atherosclerosis denotes a pathologic process primarily affecting the intima of larger arteries and characterized by focal thickening in which stainable lipids can be demonstrated in and between the cellular elements. The lesions have shown at one extreme almost exclusive fibrous composition with none or only minimal lipid material, while, at the other extreme, they contain lipid

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accumulations of massive proportions. Based on these widely different appearances, 2 schools of thought have emerged regarding the primary nature of this atherosclerotic process: [1] that the first change consists of hyperplasia of the intima with secondary fat absorption, and [2] that the fatty deposit is primary and in turn stimulates the formation of connective tissue.

Virchow[2] in 1856 published one of the earliest descriptions of the atherosclerotic process, suggesting that the earliest change was an increase in intimal connective tissue resulting from mechanical irritation of the intima by the pressure of the blood at critical points. He felt that the thickened intima then interfered with the nutrition of the intimal cells which depend for their sustenance on the plasma of the circulating blood. Degeneration of the thickened intima then occurs at points most remote from its inner lining, resulting in fatty degeneration or calcification of the connective tissue elements. Ceelen,[8] Tuthill,[9] and Dörfler[10] reported on large series of cases, and all agreed that hyperplasia of the intima was the first and often the only change in atherosclerosis.

The second theory, referred to as the filtration theory, is that atherosclerosis is primarily a disease of fat absorption and that this lipid material, once deposited in the intima, stimulates the growth of connective tissue as the first step in the formation of an atheromatous plaque. This concept was first suggested in 1939 by Aschoff,[11] who felt that atherosclerosis was a trophic vascular disturbance closely connected with wear and tear occasioned by advancing age. Aschoff, along with Duff and McMillan,[12] also felt that these fatty deposits were derived from the blood lipids and that they first appeared in the form of fine droplets deposited between the intimal connective tissue lying adjacent to the internal elastic membrane. Leary[13] insisted that the fatty deposits were carried into the arterial intima in phagocytic cells from the liver and were not introduced as free lipids. Regardless of how the fat is deposited in the intima, these investigators agreed that the presence of the fatty material stimulates the growth of connective tissue as the first step in the formation of an atheromatous nodule. If this latter concept is correct, it certainly would suggest that nutritional factors might be of great importance in at least the initiation of atherosclerosis.

In an effort to determine which of the above concepts is correct, histologic examination was made of 500 large arteries of the circle of Willis in order to trace the development of this atherosclerotic process. Certainly, the most consistent and earliest vessel change was the deposition of a light-staining fibrillar material within the intima which separated the endothelial lining from the elastica interna. This material at no time could be stained with fat stains. It soon increased in thickness and assumed a strand-like structure that accepted the connective tissue stains. This collagenous proliferation was often the only tissue change observed and, in many vessels, was present without any associated fatty deposits. It was the predominant type of alteration observed within many of the smaller arteries of the circle of Willis. Even in the larger arteries, this intimal connective tissue often produced focal extensions into the media and was free of fat. When fairly extensive, deposits of fatty material appeared deep between the connective tissue spaces. The fatty deposits ultimately degenerated into cholesterol crystals, some of which soon were replaced by areas of calcification.

Our observations tend to support the concept that the primary tissue change in atherosclerosis is an intimal connective tissue change and that the fatty alterations are secondary in nature. This is based on a number of specific observations: [1] The most consistent and earliest vessel change is the proliferation of intimal connective tissue. [2] This tissue does not stain early with fat stains. [3] The intimal connective tissue increase was often the predominant and only alteration present, particularly within some of the smaller vessels of the circle of Willis. [4] Even in larger arteries where fatty deposits were encountered, the connective tissue proliferation within the intima was often seen in areas where no fatty substance was present.

WEIGHT AND ATHEROSCLEROSIS

Beginning in the third decade of this century, extensive analyses of life insurance statistics suggested a positive correlation between

obesity and atherosclerosis. Notable among these studies is that of Dublin,[14] who found the death rate from organic diseases of the heart and diseases of the arteries to be approximately twice as frequent among obese men as among those underweight. Blotner,[15] in reviewing coronary scleroses, found the incidence of obesity to be 4 times more common in those patients with coronary sclerosis. French and Dock[16] observed obesity in 91% of 80 soldiers between the ages of 20 and 36 years who had fatal coronary heart disease. In 1953, Master, Jaffe, and Chesky,[17] in a clinical study, concluded that coronary disease was much more common in the obese male patient than in the control, although they reported that the factor of weight did not seem to play a similar role in the female. Roberts, Cambel, and Wilkins,[18] using a special grading system, found a significant increase in the occurrence of both hypertension and obesity in male patients suffering from severe involvement of the aorta and coronary arteries. Although the hypertensive patients were more often obese than were the normotensive individuals, the authors did not feel that the hypertension in the obese population exerted an additive effect on the degree of atherosclerosis in the various arteries. They felt that the obesity itself played an important role in accentuating the atherosclerosis.

In spite of the implications of the above studies, Weiss and Minot,[19] after an extensive review of the literature, concluded that there was little evidence that overnutrition leads to atherosclerosis in man. These authors pointed out that hypertension is commonly present in obese individuals and that the elevated blood pressure was probably the active factor in the increased atherosclerosis in obese individuals rather than the nutritional element itself. The close relationship between hypertension and obesity, of course, has been observed for many years.[20,21] Faber and Lund,[22] in studying atherosclerosis in 408 aortas on the basis of weight and cholesterol content of the blood, concluded that hypertension caused a rise in both factors. Wilens[23] reviewed the atherosclerotic changes in 1,250 routine autopsies and concluded that, although hypertension did increase the incidence and severity of atherosclerosis, it did so in both underweight and overweight individuals. Therefore, he concluded that the factor of hypertension operated independently of weight. Wilens implied that obesity itself may contribute to the development of atherosclerosis, yet, of his normotensive males with severe atherosclerosis, almost half were underweight, suggesting that the factor of obesity probably was less significant than indicated by the author.

Dawber, Moore, and Mann,[24] in a four-year prospective study of the Framingham group, found a similar apparent relationship between obesity and arteriosclerotic heart disease but concluded that much of this correlation was on the basis of hypertension associated with obesity.

Even when the factor of hypertension is not excluded, a number of investigators have observed no increased incidence of obesity in the various forms of vascular disease. Root and Sharkey[25] found that obesity maintained about the same relationship to patients with coronary disease as for control groups. Yater and his associates[26] found no significant difference in the induction weights of 233 men dying of coronary artery disease as compared to the weights of all inductees during World War II. Rosenthal,[27] in studying the aorta in 500 individuals of all age groups, observed that the average weights of those with severe atherosclerotic changes were not significantly greater than those with smooth aortas.

It is apparent from this survey of the literature that there is still considerable question regarding the significance of obesity to the development of atherosclerosis. For this reason, we felt that a study of our cases might offer some information as to the possible influence of weight upon the atherosclerotic process implicating the cerebral arteries. The standard used for the determination of the weight status of the patients was that published by Lindberg and his associates.[28] This is a fairly liberal standard in which 10% is allowed on either side of the normal weight for that particular height before a person is considered to be over- or underweight. Tables 1 and 2 show the incidence of cerebral atherosclerosis as compared to the patient's weight. Apparently the onset of the atherosclerotic process is not influenced significantly by the patient's weight (Table 1). The percentage of patients that show no cere-

TABLE 1
WEIGHT RELATED TO THE ABSENCE OF CEREBRAL ATHEROSCLEROSIS

Age	Overweight			Underweight		
	Unaffected	Total	Per cent	Unaffected	Total	Per cent
21-30	7	7	100	10	10	100
31-40	6	7	86	12	15	80
41-50	22	32	68	24	32	75
51-60	32	78	41	23	52	44
61-70	13	64	20	29	89	33
71-80	7	59	12	11	87	13
81-	0	16	0	4	59	7

TABLE 2
WEIGHT RELATED TO SEVERE CEREBRAL ATHEROSCLEROSIS

Age	Overweight			Underweight		
	Affected	Total	Per cent	Affected	Total	Per cent
21-30	0	7	0	0	10	0
31-40	0	7	0	0	15	0
41-50	2	32	6	2	32	6
51-60	16	78	20	4	52	8
61-70	31	64	48	22	87	25
71-80	26	59	44	50	87	57
81-	11	16	69	46	59	78

bral atherosclerosis is comparable in all age groups in both overweight and underweight individuals. This strongly suggests that this particular nutritional factor plays no role at least in the initiation of this degenerative vascular process.

Even though it appears that obesity does not influence the development of atherosclerosis, it is possible that, once this process begins, it may be accelerated by nutritional disturbances. If this were true, one might anticipate that severe cerebral atherosclerosis would be more frequently encountered in obese individuals. From Table 2 and Figure 1, it is apparent that weight plays little role in even severe atherosclerosis except for the sixth and seventh decades of life, when severe atherosclerosis apparently increases 2 to 2½ times in obese individuals. Peculiarly enough, this trend is reversed in the eighth decade where severe atherosclerosis is more frequent in underweight individuals. This apparent shifting influence of weight on severe atherosclerosis in these age groups would suggest that some additional factor besides weight alone may be playing a role. From previous observations as well as studies in the literature, one of the most important associated factors to be considered is hypertension, and, from our own previous studies, it is apparent that hypertension does play a role in accentuation of the cerebral atherosclerotic process.[29] It is important, therefore, to determine whether the abrupt increase in the intensity of the atherosclerosis in the sixth and seventh decades in obese individuals might not be due to the associated hypertension rather than to the obesity. Table 3 shows the incidence of hypertension in patients of various weight status with severe atherosclerosis. It is readily apparent that, in the sixth and seventh decades, there are many more patients with hypertension in the overweight group. It is our belief that this factor probably accounts for the apparent rather than real influence of obesity on severe atherosclerosis in these decades of life.

Our data would indicate that weight plays no role in either the initiation or in the accentuation of cerebral atherosclerosis.

MALIGNANCY AND CEREBRAL ATHEROSCLEROSIS

Although there is abundant literature relating the nutritional state to the incidence and severity of atherosclerosis, relatively little has been written concerning the influence of wasting disease on atherosclerosis. Wilens[30] alluded to this in 1947 when, in a series of 104 cases, he reported less severe degrees of atheroscle-

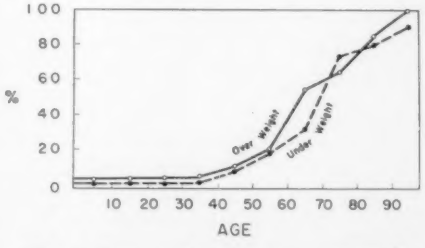

Fig. 1. Severe atherosclerosis as compared to body weight. Note there is little difference between these 2 weight curves with exception of sixth and seventh decades, where overweight individuals appear to predominate in degree of severity of atherosclerosis.

TABLE 3

INCIDENCE OF HYPERTENSION IN SEVERE CEREBRAL ATHEROSCLEROSIS

Age	Overweight			Underweight		
	Affected	Total	Per cent	Affected	Total	Per cent
51-60	10	15	70	1	15	7
61-70	19	52	35	12	52	23
71-80	19	71	26	21	71	30
81-90	5	33	15	9	33	29

rosis in the aorta and coronary arteries of individuals dying with terminal weight loss. Although the underlying cause of weight loss in his 39 cases was not given, it is presumed that most of them were victims of wasting disease. In 1951, Wanscher, Clemmesen, and Nielson[31] demonstrated less pronounced atherosclerotic lesions in patients suffering from carcinoma than among persons without cancer. Lober[32] in 1953 studied the hearts of 536 cases at autopsy and concluded that the degree of coronary sclerosis in persons dying with malignant neoplasm was significantly less than in those free of malignancy.

TABLE 4

RELATIONSHIP OF MALIGNANCY TO ABSENCE OF CEREBRAL ATHEROSCLEROSIS

Age	General population			Malignancy		
	Unaffected	Total	Per cent	Unaffected	Total	Per cent
0-10	107	107	100	11	11	100
11-20	30	33	91	4	4	100
21-30	32	33	97	8	8	100
31-40	50	60	84	12	12	100
41-50	84	116	72	39	44	88
51-60	118	232	51	59	87	70
61-70	80	287	28	31	91	34
71-80	30	272	11	12	77	16
81-	7	135	5	1	21	5

In the present series of 1,175 cases, there were 364 patients dying with malignant disease. An analysis of the atherosclerotic process in these individuals as compared to that of the total series is impressive (Table 4, Fig. 2A and B). Our findings indicate that persons with malignancy tend to have cerebrovascular disease at a later age and that the changes when present are usually less severe than in the general population. In the total series of cases, the atherosclerotic process first appears in the second decade of life at which time 9% of individuals show some degenerative changes in the intima. In contrast, patients with malignancy show no cerebral atherosclerosis until the fifth decade of life (Table 4). A comparison of the incidence of severe atherosclerosis is also revealing (Table 5). In the total series, severe atherosclerosis first appears in the fourth decade of life. Yet severe atherosclerotic changes are not found in patients with malignancy until the seventh decade. Furthermore, in each age group, severe atherosclerosis is much less frequent in the malignancy group than in the general population. Advocates of the view that obesity predisposes to the development of atherosclerosis will probably feel that this inverse relationship between malignancy and atherosclerosis is simply a reflection of the fact that individuals suffering from malignancy tend to be underweight at the time of autopsy. Yet, in our series, only 40% of those patients with malignancy were actually underweight. Furthermore, in this same study of 1,175 cases, we feel that we have presented

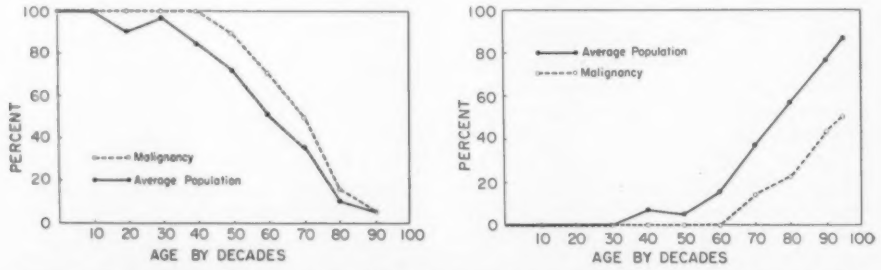

Fig. 2. Comparative study of atherosclerosis in patients with malignancy: [A, left] no cerebral atherosclerosis. [B, right] severe atherosclosis

adequate evidence to show that obesity itself has no significant relationship to atherosclerosis.

There have been convincing studies dealing with the rather low incidence of atherosclerosis in economically underdeveloped countries and in groups subjected to the famine of war. Notable among these reports is that of Malmos,[33] who demonstrated that the mortality from vascular disease declined in Finland, Norway, and Sweden during the "lean" years of the war. However, this author suggested that not only the quantity but also the qualitative composition of the diet has a bearing on the origin of atherosclerosis. The present study suggests that malignancy may influence metabolism regardless of weight loss, thereby influencing the extent of atherosclerosis. The exact mechanism by which this may occur must depend on a clearer understanding of the metabolism of patients with malignant disease.

Our studies show that patients with malignant disease are several decades behind the no-malignancy group in regard to the severity of atherosclerosis (Fig. 2A and B). This suggests that wasting disease may actually cause a regression of the atherosclerotic process rather than simply slowing its development once it has begun. Indeed, Aschoff, as early as 1924,[34] was convinced that atherosclerosis was a reversible process. More recently, investigators have demonstrated its reversibility in animals. Regression of atherosclerotic plaques have been shown in the dog by Bevans, Davidson, and Kendall[35] and in the chick by Pick and his group.[36] Finally, Rivin and Demitroff[37] have shown less coronary atherosclerosis in elderly males receiving estrogen therapy for prostatic carcinoma in comparison with a control group receiving no hormone. The implications of these studies are self-evident. Indeed, they warrant much more intensive clinical, pathologic, and experimental investigation, for such studies might give better insight into the etiology and management of degenerative vascular disease.

TABLE 5

RELATIONSHIP OF MALIGNANCY TO SEVERE CEREBRAL ATHEROSCLEROSIS

	Average population			Malignancy		
Age	Affected	Total	Per cent	Affected	Total	Per cent
0-10	0	107	0	0	11	0
11-20	0	33	0	0	4	0
21-30	0	33	0	0	8	0
31-40	4	60	7	0	12	0
41-50	6	116	5	0	44	0
51-60	36	234	16	0	67	0
61-70	107	287	37	13	91	14
71-80	156	272	57	17	77	22
81-	106	135	78	10	22	45

DIABETES AND CEREBRAL ATHEROSCLEROSIS

Although it has been fairly well proved that diabetes does accentuate atherosclerosis, particularly of the coronaries, kidneys, and extremities, little has been written regarding its influence on the cerebral blood vessels. Since the basic atherosclerotic process is similar in the coronary and larger cerebral vessels, it would be very important etiologically if such a difference actually occurred. Most of the detailed studies on diabetes and atherosclerosis have been carried out on the coronary vessels. It seems definitely proved in numerous careful pathologic studies that coronary atherosclerosis occurs about twice as frequently in diabetic patients than in nondiabetic persons above the age of 40 years. Root and his associates[38] in 1939 reported on 2,626 autopsies of which 316 were diabetic persons. Atherosclerosis occurred in 56% of the latter as compared to 29% of the normal controls. Similar observations on the coronary vessels have been reported by Blotner,[15] Nathanson,[39] Lisa and associates,[40] and Millard and Root.[41] In the normal population, coronary disease is reported to be 3 times as frequent in males as in females. In diabetic persons, the ratio changes to 1:1 due to the marked increase in diabetic females who show coronary atherosclerosis.[16,39,40]

Even though most attention has been devoted to the effects of diabetes on the coronary vessels, it is apparent that this metabolic disease does affect the vascular system generally. Bell,[42] for example, reported generalized atherosclerosis to be almost twice as frequent in the diabetic patients among 4,979 patients over 40 years of age. In this series, Bell found that encephalomalacia was twice as great in diabetic persons.

In contrast to the extensive pathologic studies on coronary atherosclerosis as related

to diabetes, practically no studies have been recorded on the cerebral vessels. A few clinical observations have been reported by Joslin and associates,[43] Warren and LeCompte,[44] and Bell,[42] all of whom have been impressed by the relative increase of clinical cerebrovascular disease in diabetic persons when compared to normal individuals. Since these studies have been based on clinical manifestations of vascular occlusion, they offer little information on the true incidence of atherosclerosis because vascular occlusion often is the result of thrombosis in the presence of minimal atherosclerosis.

It was felt that our material might offer some definite conclusions as to the influence of diabetes on cerebral atherosclerosis, since in all our cases detailed studies were made of the actual pathologic vascular process. Of our 1,175 patients, 65 were diabetic. Table 6 compares the frequency of cerebral atherosclerosis in diabetic persons and in the general population. It is readily apparent that diabetes does accelerate the development of atherosclerosis in cerebral vessels just as it does in other vessels in the body, particularly in persons between the ages of 40 and 60 years.

DISCUSSION

In spite of extensive studies in both man and animal, the role of nutrition in atherosclerosis remains unanswered. Virchow, who first described this process, recognized the fatty changes in these lesions but felt that they were secondary in nature. He suggested that the earliest alterations consisted of an intimal connective tissue proliferation resulting from mechanical irritation by pressure of the blood at critical points. He felt that this thickening of the intima then interfered with nutrition of intimal cells, causing tissue degeneration with liberation of cholesterol and other fats. Aschoff and Marchand reviewed Virchow's work and felt that functional wear and tear or excessive stresses cause a loosening of the ground substance of the intima, which enables cholesterol to enter the altered intima together with the plasma of the vascular lumen, and that this fat is retained and causes the intimal connective tissue proliferation. It was felt by these authors that the quantity of lipid that accumulates in the atherosclerotic lesions was so large as to preclude the possibility that they originate from a simple breakdown of tissue in the intima.

This early interest in the role of lipids in atherosclerosis was intensified by the observations that a state of hypercholesteremia preceded and accompanied the development of experimental atherosclerosis in rabbits. Anitschkow was convinced that the experimental lesions were identical with those in man. In his early lesions, there invariably occurred an accumulation of lipid in the intercellular substance of the intima followed later by macrophages filled with fat. However, Anitschkow had considerable difficulty reproducing the more chronic lesions observed in man in which connective tissue changes predominate. Invariably, in the experimental animal, the vascular lesions show a predominant lipid composition and connective tissue changes are limited or entirely absent. Anitschkow admitted that his lesions in rabbits did not contain well-defined layers of connective tissue proliferation, but he felt that this difference was purely quantitative and was due to the fact that in rabbits, under normal conditions, connective tissue elements are lacking in the

TABLE 6

DIABETES RELATED TO SEVERE CEREBRAL ATHEROSCLEROSIS

Age	No atherosclerosis						Moderate to severe atherosclerosis					
	Diabetic			General population			Diabetic			General population		
	Unaffected	Total	Per cent	Unaffected	Total	Per cent	Affected	Total	Per cent	Affected	Total	Per cent
21-30	1	2	50	32	33	97	2	4	50	0	33	0
31-40	1	4	25	50	60	83	1	6	17	4	60	6
41-50	1	6	17	84	116	72	2	8	25	6	116	5
51-60	2	8	25	118	232	51	16	21	76	36	232	16
61-70	3	21	14	80	287	28	12	18	67	107	287	37
71-80	2	18	11	30	272	11	4	6	66	156	272	57

inner layers of the aortic wall. On the basis of these studies, Anitschkow felt that he had established experimental proof that the primary process in atherosclerosis was a lipid infiltration of the arterial wall with secondary reactive hyperplasia of the fibrous elements.

Certainly, our own studies and those of many other investigators strongly refute this contention. There is little doubt, to us at least, that the atherosclerotic process in the cerebral vessels is primarily a connective tissue change and often remains exclusively a collagenous reaction with no fatty component. It is difficult to correlate such changes with the lipid infiltration theory of Aschoff, Marchand, Anitschkow, and others. From the description of the morphology of the experimental lesions, there is considerable doubt whether they actually represent the same lesions seen in man. At any rate, in spite of all the experimental and human studies on atherosclerosis, one still cannot positively state [1] whether the lipid changes and the connective proliferations necessarily form a sequence and [2] whether the fatty changes in atherosclerosis form a true degeneration or an impregnation with lipid-containing blood plasma.

Although Hartroft and Thomas[45] feel that fat is present in early lesions, they conclude that there is no morphologic proof whether the lipid deposits are primary initiating events or secondary sequelae in the pathogenesis of atherosclerosis. Duff and McMillan[12] found that, while atherosclerotic lesions in the aorta and coronaries are predominantly fatty, those in other parts of the body are mainly fibrous. They also point out that the patchy distribution of atherosclerotic lesions, both in regard to the various parts of the body and of any particular vessel, strongly implies the importance of local factors, for, indeed, the blood bathing the vessels is the same throughout the body. Gubner and Ungerleider[46] point out that this lack of uniformity in the atherosclerotic process may well be related to variation in intravascular pressure. They cite the susceptibility to atherosclerosis of the left anterior descending coronary artery, the aortic arch proximal to coarctation, and the pulmonary arteries in cor pulmonale, as well as vessel segments which are fixed at points of bifurcation and immobilized by bony structures.

There is no doubt that even to produce experimental atherosclerotic lesions in animals a markedly abnormal diet is necessary. The diets which led to atherosclerosis in rabbits were not only unbalanced but were also abnormal to the animals. The one consistent factor in these experiments was that hypercholesteremia was necessary to produce the vascular lesions. However, numerous investigations have failed to demonstrate that hypercholesteremia is essential to the development of human atherosclerosis. In the vast majority of cases of severe atherosclerosis, the blood cholesterol levels are normal.[47,48] Of particular interest in this regard is the finding that cholesterol and fatty acids can be synthesized in aortic tissue,[49,50] and the suggestion has been made by Zilversmit[51] that the major amount of phospholipid in atherosclerosis plaques is synthesized in the arterial tissue rather than being derived from the plasma.

The effect upon the development of atherosclerosis of generalized metabolic disturbances caused by overnutrition and undernutrition has also received considerable attention. There is no conclusive evidence that chronic over- or undernutrition dependent upon caloric intake has any influence on the development of atherosclerosis in animals. From our own studies, one can draw similar conclusions for man. Although there is considerable clinical and pathologic evidence to suggest that obese individuals are more prone to atherosclerosis and its consequences,[14,16,23] our studies certainly indicate that the weight factor alone is of no significance. Much more important than obesity was the associated hypertention that accompanies the excess weight. When one corrects for this factor of hypertension, one finds that weight plays little role in cerebral atherosclerosis and that this process shows no differences in individuals who are underweight when compared to those overweight.

Probably the most striking observation in our study was the apparent reduction in the frequency and intensity of atherosclerosis in patients with all types of malignancy regardless of their state of nutrition. This is not a new observation and has frequently been commented upon by pathologists. Actually,

individuals dying of malignancy had much less cerebral atherosclerosis than would be expected had the atherosclerotic process stopped at the time of onset of the malignancy. This can lead to only a limited number of conclusions: [1] that individuals who do have malignancy have an inherent protection against the atherosclerotic process or [2] that malignancy causes some type of change that results in regression of the atherosclerosis already present.

It has been observed that, in certain diseases such as diabetes, hypothyroidism, and hypercholesteremia, there is often an associated hypercholesteremia and an increase in the atherosclerotic process. There is no doubt from our studies that diabetes in the older age group tends to greatly accelerate the atherosclerotic process. Joslin felt that an etiologic factor may well be an excess of fat in the body tissues and in the blood stream, since in diabetics the fat and the cholesterol content of the blood are frequently elevated. Unfortunately, in our cases, we did not have adequate blood cholesterol studies to arrive at any conclusions concerning this factor in either our general population or the diabetic persons. This problem will have to be deferred for later studies.

SUMMARY AND CONCLUSIONS

1. A study was made of the atherosclerotic process of the cerebral arteries of the circle of Willis in 1,175 consecutive autopsies in order to determine the role of nutritional factors in this degenerative vascular process. In all cases, a uniform, fairly simple coding system was used for the atherosclerotic changes so that these studies can easily be extended or compared by other investigators.

2. The primary tissue change in cerebral atherosclerosis is an intimal connective tissue proliferation; fatty alterations when present are secondary in nature. In many of the smaller vessels of the circle of Willis, the entire atherosclerotic process consists of an extensive collagenous proliferation within the intima with no associated fatty deposits. Even in larger arteries where fatty deposits are encountered, the connective tissue proliferation within the intima is often seen in areas where no fat is present. The fact that fatty deposits in cerebral atherosclerosis appear to be a late recurrence would suggest that nutritional factors probably do not play a role in initiating this atherosclerotic process.

3. Obesity appears to play no role in cerebral atherosclerosis. The atherosclerotic process first appears in the same age groups in individuals who are overweight and underweight. Obese individuals in the sixth and seventh decades of life tend to show a greater amount of severe atherosclerosis. However, in these same age groups, the obese patients had a greater frequency of hypertension than did the undernourished patients. It was felt that the increased frequency of severe atherosclerosis in these age groups was due to the hypertension rather than to the obesity.

4. Patients with malignant disease tend to have cerebrovascular disease at a later age than the general population. Moreover, when atherosclerosis occurs, it tends to be much less severe in the patients with malignancy. It is suggested that wasting diseases may actually cause a regression in the atherosclerotic process rather than simply retarding its development.

5. Diabetes tends to double the frequency and intensity of cerebral atherosclerosis in individuals beyond the fourth decade of life.

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The use of cyclohexylamines in thalamic pain

John F. Kurtzke, M.D.

THE THALAMIC SYNDROME of Dejerine and Roussy is characterized by contralateral motor and sensory disturbances due to lesions involving principally the posteroventral and ventrolateral thalamic nuclei and internal capsule; the resulting dysfunction includes hemiparesis, hemiataxia, hemisensory defect, and most strikingly, "thalamic pain." This last consists of an exceedingly unpleasant continuous painful state, usually described as burning, plus dysesthesia—spreading, poorly localized exacerbation of the pain in response to tactile or noxious stimuli. Lesions of the thalamogeniculate branch of the posterior cerebral artery are the most common cause of this disorder. Treatment for this painful state has been most unsatisfactory; efficacy of chlorpromazine[1] has not been confirmed.

In September 1958, Greifenstein and associates[2] reported on the use in anesthesia of a unique compound, Sernyl or CI 395, a cyclohexylamine which was found to produce analgesia without loss of consciousness. The intravenous use of 0.2 mg. per kilogram caused "complete insensibility of pain" often associated with amnesia but without overt stupor. The site of action was considered to be at the thalamic level. With these findings, utilization of this agent in thalamic pain seemed appropriate, and Stevens[3] in fact stated that unpublished observations supported its efficacy in this state. Available for trial were 3 compounds of this series: CI 395, CI 400, and CI 401.

CASE REPORT

A 64-year-old right-handed white male was admitted to this service on September 22, 1958, with pain in the left leg for nineteen months. Except for angina pectoris for eight years, he was in good health until November 7, 1956, when right hemiparesis developed suddenly, subsided completely within six weeks, and then recurred for two days. On January 3, 1957, there was onset of diplopia, to which were added dysphagia and dysarthria four days later. These symptoms persisted for several months.

In February 1957, the patient noted gradual onset of a constant burning pain in the left foot, which in two months had spread to the entire left lower limb. In February 1958, similar but milder pain in the left hand began. Any local stimulus including clothing aggravated the pain, as did walking or Valsalva maneuvers; only narcotics relieved this state. For the last six months before admission, there was no change in his condition. On September 1, 1957, he had had upon awakening left hemiparesis which lasted for two hours.

On admission, the patient had hyperreflexic mild right hemiparesis with Babinski sign, impaired upward gaze, and diminished perception over the left lower extremity for light touch, pressure, pinprick, heat, and cold, with a hyperalgesic dysesthesic response to testing of each of these modalities. Minimal dysesthesia and incoordination of the left hand were also present. Usual blood chemical, hematologic, and urinary findings were normal. Spinal fluid was normal aside from a protein content of 68 mg. per cent. Usual roentgenograms were unremarkable; 2 electroencephalograms showed generalized slowing plus separate delta foci from left and right motor regions. (Laboratory data, medication, and clinical response are summarized in Figure 1.)

Chlorpromazine was administered from admission in dosage finally reaching 1,200 mg. daily. This did not alter his painful state, and the daily dose had to be reduced to 900 mg. due to obtundation and unsteadiness of gait. In this period, high doses of Darvon with aspirin and the frequent usage of codeine were necessary. In December, chlorpromazine was further lowered to 300 mg. a day and was discontinued on February 14.

On February 12, 1959, CI 401, 2.5 mg. daily, was

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This study was made possible through the courtesy of Parke, Davis & Co., which provided the medications utilized.

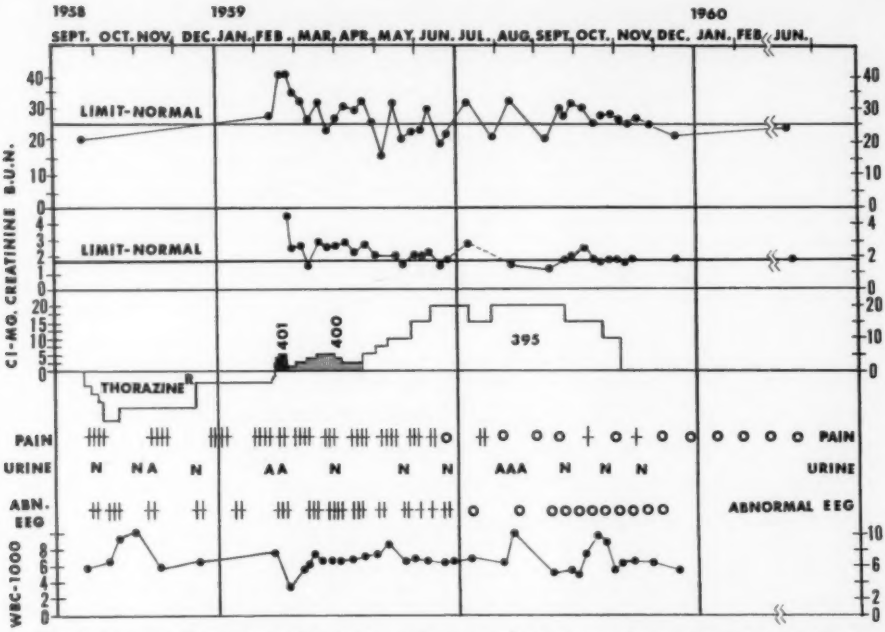

Fig. 1. Summary of pertinent data in the case presented. From top down, the scales are blood urea nitrogen in milligrams per 100 cc.; blood creatinine, milligrams per 100 cc.; medication—cyclohexylamines in mg. total daily dose (below the line is noted the chlorpromazine dosage); thalamic pain on an estimated 0 to 4+ scale of severity; urinalysis with N as normal and A as abnormal; abnormal electroencephalogram on 0 (normal) to 4+ (highly abnormal) scale; and total white blood count in thousands.

begun. Two days later, dosage was raised to 2.5 mg. twice a day, only to be discontinued on February 20 because of leukopenia (3,400 white cells with 36 per cent neutrophils) and azotemia (blood urea nitrogen, 40.5 mg. per cent and creatinine, 4.5 mg. per cent). Electroencephalogram showed greater slowing than previously. On February 21, CI 400 at 1.25 mg. daily was started. Whereas the patient had reported lessening of pain and used fewer analgesics with CI 401, he noted its recrudescence then, so that CI 400 was increased to 1.25 mg. twice a day on February 27 and to three times a day on March 7; from March 11, CI 400 was given at 2.5 mg. twice daily. Due to borderline elevations in blood urea nitrogen and even more marked electroencephalographic changes, the dose was lowered to 3.75 mg. a day on March 29, and medication was discontinued April 1. Over this period, there was equivocal improvement in his pain state; he blandly agreed he had intolerable pain but less often requested analgesics. However, he still was attired in light shorts and slippers and kept bed clothing off his limbs, despite the winter weather.

On April 1, CI 395 was instituted at 2.5 mg. once daily and was gradually increased to 5 mg. four times a day on June 5. This dosage was continued after his discharge on June 26, 1959. His pain was gone; occasional "tingling" of the leg was his sole complaint. He used no analgesics, wore appropriate clothing, and had regained the 30 lb. he had lost. Over this period, occasional borderline elevation of urea nitrogen and creatinine was noted, but the electroencephalograms had become essentially normal.

The patient returned to hospital on July 4, 1959, because of dysarthria and left hemiparesis occurring that same day. He demonstrated a pronounced dysarthria, nasal regurgitation, dysphagia, diminished gag reflex, weak right soft palate, mild quadriparesis more marked on the right, impaired sensation of the left limbs, and recurrence of the thalamic pain. Dicumarol was given. CI 395 dosage was reduced to 15 mg. total daily on July 8, since blood urea nitrogen was 33 mg. with creatinine 2.8 mg. Except for the pain which persisted unchanged, his clinical state improved rapidly; he had attained his prior neurologic status by July 24. Due to the pain, on that date CI 395 dosage was returned to

5 mg. four times daily. Shortly after, the pain subsided and he was discharged August 12, with the cited dose of CI 395 and 75 mg. of Dicumarol daily.

The patient was again admitted to the hospital on September 21, 1959, due to confusion and paranoid ideation for the previous two days. He was disoriented and had impaired memory and short attention span. CI 395 was reduced to 15 mg. daily then and to 10 mg. on October 19 because of persistent obtundation and urinary incontinence. The drug was discontinued on November 2, 1959. In November 1958, before the use of these agents, psychiatric evaluation had revealed him to be a mentally intact individual of above average intelligence without evidence of brain damage, neurosis, or psychosis. In contrast, on October 15, 1959, psychologic tests showed full scale IQ 63, verbal 72, and performance 56; Wechsler Memory Scale was too poor to score. Repeat testing on November 10 revealed a verbal IQ of 88 and Memory Scale of 74. The patient became more alert after cessation of CI 395 but did complain mildly of intermittent tingling pain in the left arm. Paranoid ideation and disturbed behavior persisted, however, so he was transferred to the Psychiatric Service in December 1959. This state slowly abated, and he returned to Neurology in March 1960. Psychologic tests in May and July 1960 revealed a full scale IQ of 83 (verbal 86 and performance 81) and Memory Scale of 77; projective tests did not indicate overt psychotic thinking.

The patient was discharged August 2, 1960. He walked without aid and was well-oriented, cooperative, and comfortable. He would admit to some pain in the left leg when directly questioned, but this did not manifest itself objectively. The anticoagulants were continued as sole medication.

DISCUSSION

This elderly man had basilar artery insufficiency with, as its most disabling feature, a thalamic pain state for one and one-half years. Chlorpromazine to toxicity did not alter this state. CI 401 at 5 mg. daily seemed to improve the condition but had to be discontinued due to leukopenia and azotemia after only eight days of therapy. CI 400 was given for forty days also at a maximal dose of 5 mg. and did produce some amelioration of pain but was stopped because of borderline azotemia and more abnormal electroencephalograms. CI 395 led to disappearance of the thalamic pain with the high doses of 20 mg. a day; 15 mg. on 2 separate occasions was but partially effective. A severe delirioid response with residual brain damage took place after five months' use of this drug. While it is true this could have been due to progression of his basic vascular disease, the temporal relation with drug use and improvement with drug withdrawal is suggestive. In the ten months following cessation of cyclohexylamine usage, the thalamic pain has not recurred. Explanation for this (and indeed for the pain itself) is not clear, but the possibility of "breaking up" abnormal reverberating circuits involving the thalamus should be considered. The dose-related therapeutic response noted above is some evidence against this being a coincidental finding. The patient was his own control, and many other agents had been administered without avail before this by us and others. In addition, alleviation of thalamic pain is not a common placebo response; the usual experience in treating this disorder warrants attention to apparent efficacy in even one instance.

The cyclohexylamines utilized included Sernyl or CI 395 (l-[l-phenylcyclohexyl] piperidine monohydrochloride), CI 400 (N-ethyl-l-phenylcyclohexylamine monohydrochloride), and CI 401 (1-phenylcyclohexylamine monohydrochloride). The chemical differences consist of substitutions on the amine group of CI 401, with an ethyl radical comprising CI 400 and a piperidine ring, CI 395 (Fig. 2). Using equal amounts (milligrams) of each agent, it appears—in this case at least—that CI 401 is the most potent but also the most toxic and, again in the present instance, that the therapeutic index is greatest though still slim with CI 395.

With CI 395, Meyer, Greifenstein, and De Vault[4] stated that "this drug is presumed to have a relatively selective action on sensory cortex, thalamus and midbrain." They gave 80 subjects this agent intravenously in doses of up to 10.5 mg.; "thirteen developed a confusional psychosis of 12-72 hours' duration characterized by feelings of unreality, depression, anxiety and delusional and illusional experience;" 22 patients with varied neurologic disorders were given 7.5 to 12.5 mg. a day orally, and 8 "showed evidence of impaired mentation." The intravenous usage was found to cause diffuse slowing in the electroencephalogram in the higher doses, and, in healthy volunteers, hypertension and increased respiratory minute volume (depth and rate) were found. These authors further noted the success-

ful use of Sernyl in 4 patients with thalamic pain, but details were not provided.

Luby and associates,[5] utilizing intravenous doses of 0.1 mg. of CI 395 per kilogram in 9 normal and 9 schizophrenic individuals, reported alterations in body image, feelings of estrangement, and disorganization of thought processes in all the subjects, with many showing drowsiness and hypnagogic phenomena. All subjects demonstrated diminution of pain, touch, and position sense, rotatory nystagmus, and ataxic gait, findings also reported by Meyer and associates.[4]

Feldman[6] gave 20 to 80 mg. a day of CI 401 to 55 chronic psychotic patients. "The laboratory reports [of "renal, hepatic and hemopoietic functions"] were characterized by sporadic and unpredictable abnormal readings, completely unrelated to any clinical findings." Of this group, one-third responded with "significant clinical improvement." Bodi and associates[7] treated 32 neurotic patients with Sernyl at 1.5 to 6 mg. a day for four to six weeks; half the patients improved "moderately" or "markedly." Varied side effects, including drowsiness, syncope, staggering gait, vivid dreams, and maculopapular rash, were noted in 10 patients.

Riffin[8] considered that CI 395 and CI 400 were not advisable in anesthesia due to "the unpredictable and capricious sensory blocking effect (and) the rather frequent and annoying post-operative side effects. . . ." Usage of CI 400 in anesthesia was also reported by Lear and associates.[9] They found a narrow therapeutic range of 10 to 20 mg. and "that increasing the dose did not produce a more intense sensory block, but rather exaggerated the undesirable postoperative side reactions (chiefly psychic). Postanesthetic emergence delirium was commonly observed."

No other published papers on CI 401 were found. According to Fisken, Reutner, and Weston,[10] high doses by all routes produce severe incoordination in rats, mice, dogs, and monkeys, with respiratory depression when lethal doses were utilized and with convulsions in dogs and monkeys. Nonlethal toxic effects were seen at 12.5 mg. per kilogram orally and at 1 to 5 mg. per kilogram intramuscularly with chronic administration in monkeys. The LD_{50} in mice

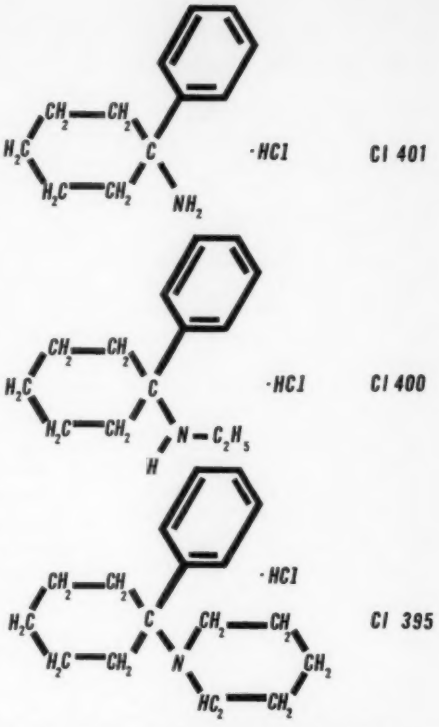

Fig. 2. Chemical formulae of the cyclohexylamines utilized in this study. The uppermost is CI 401, or l-phenylcyclohexylamine monohydrochloride. The middle one is CI 400, or N-ethyl-l-phenylcyclohexylamine monohydrochloride, and the lowermost is CI 395 (Sernyl), or l-(1-phenylcyclohexyl) piperidine monohydrochloride. The sole differences are seen to be substitutions on the amine group of CI 401.

was 30 mg. per kilogram for single intravenous doses and 195 mg. per kilogram for single oral doses. In contrast, similar LD_{50} figures for CI 400 were 21 mg. per kilogram intravenously and 118 mg. per kilogram orally, while with CI 395 the LD_{50} was 16 mg. per kilogram intravenously and 116 mg. per kilogram orally. Accordingly, CI 401 should have provided the highest level of safety; in our case, much higher doses of CI 395 were tolerated.

This fascinating group of compounds apparently does have a selective inhibitory effect

on sensory input, presumably at a central (thalamic) level. However, their usage is limited by a high incidence of other neural effects, including nystagmus, ataxia, convulsions, and electroencephalographic and mentation changes, and also by toxic effects on kidney and bone marrow. Employment of the present cyclohexylamines does not appear warranted in any condition where another agent could suffice, especially in psychiatric illnesses. In a condition such as thalamic pain, or even in other refractory pain states, their cautious administration with adequate laboratory control is justified. It is hoped that further modifications of the basic structure might provide a safer agent in this much-needed class of drugs.

SUMMARY

1. The effects of 3 cyclohexylamines were studied in a patient with thalamic pain. The compounds tested were the monohydrochlorides of, respectively, 1-phenylcyclohexylamine (CI 401), N-ethyl-1-phenylcyclohexylamine (CI 400), and 1-(1-phenylcyclohexyl) piperidine (CI 395).

2. In this patient, CI 401 caused leukopenia and uremia in only eight days; when CI 400 was given for over a month, borderline azotemia and electroencephalographic changes were found. Both of these agents seemed to lessen the pain. CI 395 given for five months did control effectively the thalamic pain without recurrence after its withdrawal. However, termination of its use was necessitated by an acute delirioid reaction with some residual brain damage.

3. Published experiences of others were reviewed; these drugs are not indicated in anesthesia due to unpredictability of response and a high incidence of psychic side effects. Their use as psychopharmacologic agents is not indicated due to lack of proved efficacy and their toxicity.

4. It is concluded that these cyclohexylamines may provide an effective but hazardous treatment for thalamic pain and that their use is warranted in this disorder with appropriate safeguards.

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A case of sudanophilic diffuse sclerosis with study of the brain lipids

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As CLINICIANS have become alerted to Schilder's disease, it has been diagnosed with increasing frequency in recent years. The present case would seem worth adding to the literature for two reasons: first, because it came under our observation early and provided an unusual opportunity to follow the clinical progress through to death and second, because the brain lipids were subjected to chemical analysis.

CASE REPORT

A 28-year-old white veteran was admitted to the hospital on January 2, 1959, as a transfer from another hospital. The history accompanying the patient related that he had been in good health except for a sore throat about six weeks previously. On December 17, he felt a pain in the midthoracic region followed by persistent mild discomfort. On the same day, he noted numbness and tingling that began in the right foot and ascended to his groin. The following day, numbness was noted in the left foot and spread similarly, reaching the level of the costal margins within a couple of days. This was accompanied by progressive loss of strength in the lower limbs, and, by the evening of December 24, he had difficulty in voiding.

At the time of the initial examination on December 26, cranial nerves and upper limbs were negative. There was considerable weakness of the lower limbs, with increase in the deep reflexes as compared with the upper reflexes, a bilateral Babinski sign, and a sensory level at D8 or 9. The sensory loss was partial and was most easily detectable with hot and cold objects.

A spinal puncture and myelogram performed on December 26 showed normal dynamics and free flow of dye throughout the entire spinal canal. Analysis of the fluid was normal except for a protein content of 87.5 mg. per cent.

The paralysis of the legs progressed, becoming complete by December 28, 1958, at which time there was a level of anesthesia below the fifth thoracic dermatome. Coincident with this, considerable confusion and impairment of memory became apparent.

On arrival at this hospital two weeks after onset, the patient displayed total motor paralysis of the lower extremities, sensory loss below the third thoracic dermatome, moderate nuchal rigidity, mental confusion, and complete cortical blindness. The disks appeared normal. The pupillary reactions to light were intact, and there were no cranial nerve palsies. He was able to converse in a somewhat limited fashion but had marked memory defect, being unable to give any details of his present illness or to recall the name of his wife or child. The reflexes were lively in the upper extremities and depressed at the knees and ankles. The Babinski sign was not obtained. There was incontinence of both urinary and rectal sphincters.

The past history obtained from the family confirmed the statements of the referring physician as to the patient's previous excellent state of health. The family history was of some interest in that his only sister, who was younger than he, had been a patient at a state mental hospital in the Midwest since childhood. On inquiry to the medical director of this hospital, it was learned that this sister carries a diagnosis of "Mental Deficiency severe with Mongolism."

Spinal puncture on admission yielded a slightly turbid fluid under normal pressure, which contained 107 white cells (75% lymphocytes), 2+ Pandy test, and 122 mg. per cent protein. It was felt that the pleocytosis probably represented a reaction to his recent myelogram, and another spinal fluid specimen two weeks later contained only 4 cells and 53 mg. protein. An electroencephalogram showed diffuse slowing in the 4 to 5 per second range of slightly greater amplitude over the left hemisphere. Other laboratory studies, including serum electrolytes, viral agglutinations, and electrophoresis of both serum and spinal fluid, were not contributory.

During his first two weeks in the hospital, the patient received antibiotics supplemented by a corticoid (Aristocort, 8 mg. twice a day). The

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clinical course was rather consistently downgrade. On March 9, he had a single grand mal convulsion and, after this, right central facial weakness was noted. He became steadily less responsive and, in the latter two to three weeks of his life, he remained completely mute except for occasional unintelligible noises suggesting irritability or anger when aroused from his stupor. Wasting of the

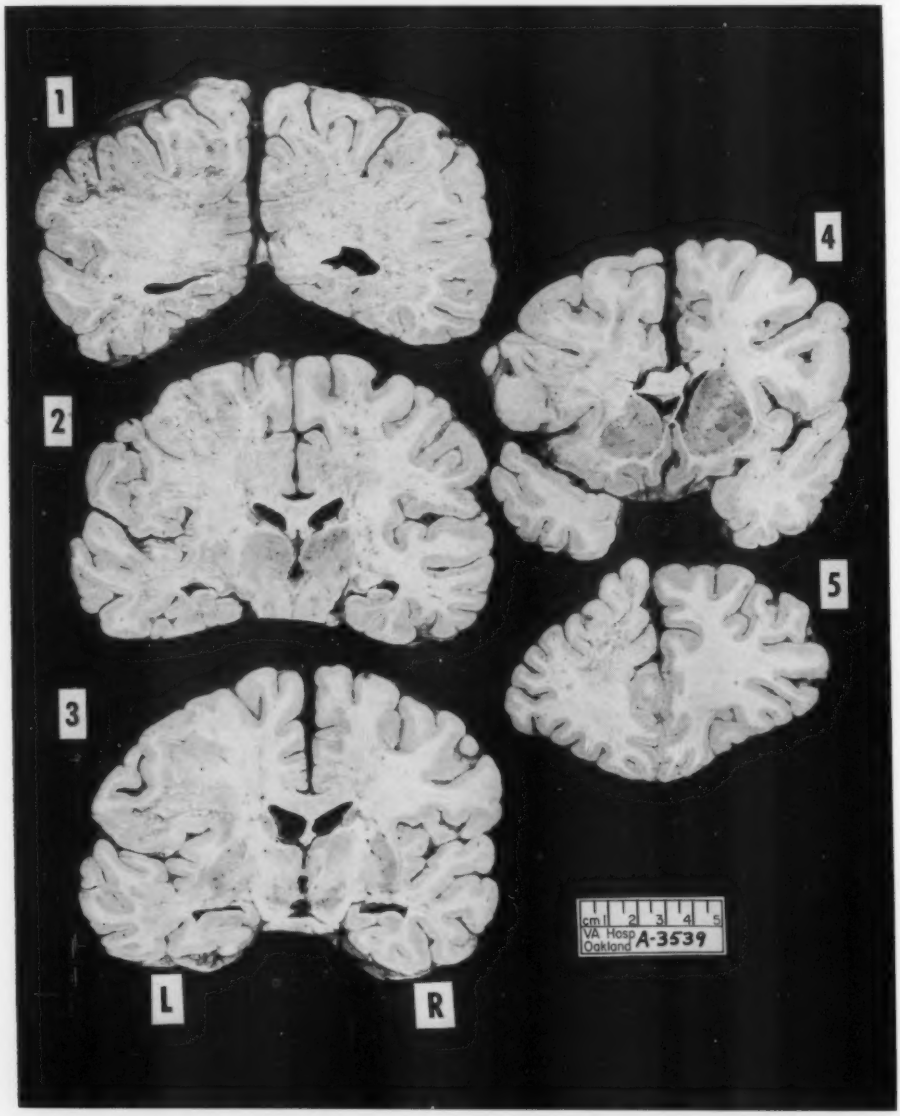

Fig. 1. Successively rostral sections of brain progressing from occipital (1) to anterior frontal lobe (5)

lower limbs became more marked and pressure sores developed over the sacrum. The right upper extremity became spastic and showed less spontaneous motor activity than the left. A urinary tract infection developed, then a terminal bronchopneumonia, and he died on April 22, 1959.

In summary, a previously healthy 28-year-old male was suddenly stricken by an acute myelopathy in the upper thoracic level. Cerebral dysfunction followed closely, dominated by cortical blindness, memory defect, and, finally, mutism and total amentia. The course was relentless and lasted approximately four months.

PATHOLOGIC FINDINGS

At autopsy, the body was markedly emaciated, weighing 110 lb. There were small decubitus ulcers over the sacrum. The bladder contained a few stones, and both acute and chronic cystitis were present. A bronchopneumonia involving the right lung was the only significant change in the remainder of the viscera, excluding the brain. The brain and spinal cord were sectioned at autopsy; a portion was taken for chemical analysis and the remainder fixed in formalin. The external configuration of the brain was not remarkable, with no gross evidence of edema. The vessels at the base appeared delicate and collapsed. The meninges were translucent and free of adhesions. The cord below the cervical enlargement appeared extremely soft. No recognizable architecture could be discerned in the cut sections from the upper thoracic region or below. From the central portion of the cord on section, there exuded a creamy necrotic material. The cauda equina presented no gross abnormality. In the cervical enlargement, there was some pallor of the posterior columns, but the differentiation between gray and white matter was preserved. On sectioning the brain, spongy softening of the white matter was seen in both occipital lobes. The immediate subcortical portions of the white matter—the so-called U fibers—appeared to be spared. As one followed the examination of the brain sections anteriorly, the destruction of the white matter became less symmetrical (Fig. 1). On the left side, the process extended forward through the central white matter to the extreme frontal pole and also involved the white matter of the temporal lobe in its entirety. On the right side, the demyelinating lesions extended no further than the midportion of the frontal lobe. The internal capsule and basal ganglia did not appear grossly involved nor did the cerebellum, brain stem, or the upper spinal cord.

Fig. 2. Occipital lobe showing giant plaque with well-defined margins and sparing of U fibers. Myelin stain. × 4

The microscopic studies included hematoxylin-eosin, oil red o, cresyl violet, Loyez, and luxol blue silver stains. There was extensive loss of myelin in the subcortical white matter with the giant plaques, as seen grossly, extending from the occipital lobes forward through the centrum semiovale (Fig. 2). Fat stains showed the presence of sudanophilic material both lying free in the tissues and within gitter cells in the demyelinated areas. The accumulation of fat-laden gitter cells in the perivascular spaces was particularly striking (Fig. 3). The disease process appeared oldest in the white matter of both occipital

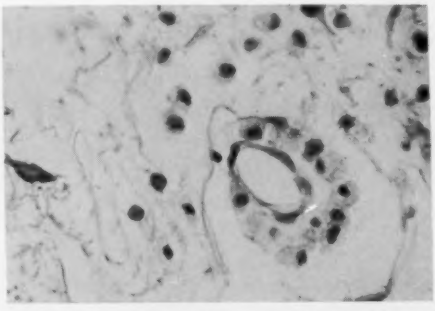

Fig. 3. Occipital white matter showing fat-laden gitter cells in the demyelinated zone, particularly clustered around perivascular spaces. Hematoxylin and eosin. × 250

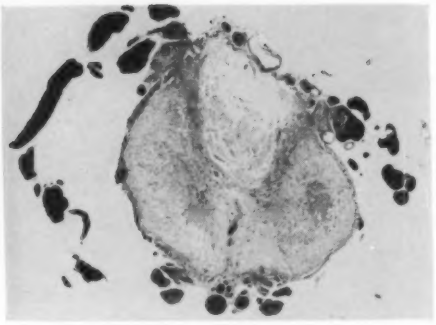

Fig. 4. Upper thoracic cord. An area of necrosis is seen in the dorsal columns. Myelin stain. × 4

lobes where cystic degeneration was noted quite extensively. Numerous astrocytes, some with large, pale cell bodies were seen in the affected areas. A few perivascular round cell accumulations were noted, but they were not a prominent feature. In some of the more anterior placed lesions, particularly in the frontal lobes, the cellularity as seen in the cresyl violet stains was quite marked and none of the spongy or cystic changes prominent in the occipital lobes was seen. In some areas, the cortex overlying the demyelinated zones appeared paler in its staining quality, and there was a mild dropping out of nerve cells and blurring of the normal cortical columnar pattern. The basal ganglia and the internal capsule were not affected. The cerebellum and brain stem likewise appeared entirely normal. The lower cervical area of the spinal cord showed extensive demyelinization in the posterior columns and, to a lesser extent, in one of the lateral columns. The oil red o stain here also showed extensive fat deposits within gitter cells in the demyelinated areas. The thoracic cord showed cavitation and distortion of the normal markings (Fig. 4). The nerve roots appeared uninvolved.

CHEMICAL STUDIES

The data available on the chemistry of primary demyelinating disease have been reviewed recently by Plum and Hansen.[1] There is general agreement that depletion of all categories of phospholipids takes place and that there is increase of neuraminic acid as well as esterification of cholesterol.

The brain tissue of this case was analyzed for phospholipids, cholesterol, polyunsaturated fatty acids (PUFA), and plasmalogens. Furthermore, fractionation of the lipids was carried out for the purpose of learning the extent of PUFA participating in the esterification of cholesterol and for possibly obtaining additional data on lipoprotein breakdown. The brain lipids of a control case without neurologic disturbances or any gross or microscopic brain lesions were subjected to similar separation. Extensive data on other control and pathologic brains are being published elsewhere.[2]

METHODS

Unfixed brain tissue was extracted and lipid phosphorus, cholesterol, water content, and PUFA were determined, as described elsewhere.[2] For titration of fatty acids, Albrink's method was followed except that the hydrolysis period was extended to two hours. Separation of the lipids into 3 fractions (cholesterol esters, free cholesterol and glycerides, and phospholipids) was accomplished by chromatography on a silicic acid column according to Hirsch and Ahrens.[3] The temperature was kept at 20 to 25° C., so that solvent activated enzymic degradation was avoided.[4]

RESULTS

Comparison of the data on this case with those obtained on the controls (Table 1) reveals depletion of phospholipids in the white and, to a lesser degree, in the gray matter. A substantial part of the cholesterol of the white matter was esterified. The PUFA levels were similar to those found in the controls; but it should be kept in mind that large amounts of lipids, though removed from their normal sites, were still present in the form of stainable lipid aggregates within the macrophages.

The plasmalogens (Table 1) of the gray matter were within the range of the controls and that reported in the literature,[5] but those of the white matter were reduced in quantity to a greater extent than the phospholipids at large.

The individual PUFA (Table 2) were determined on extracts of tissue as secured at the

TABLE 1
LIPID CONTENT OF BRAINS

		Gm./100 gm. wet weight				Plasmalogens in μm/100 gm. wet weight	Water in %
		Phospholipid	Cholesterol		Total PUFA		
			Total	Free			
Patient:							
Gray matter	(a)	2.75	1.79	1.79	.94	807.2	72.5
	(b)	2.75	1.50	1.15	.68		
White matter	(a)	2.55	3.24	1.56	.82	926.5	67.2
	(b)	2.55	2.90	1.15	.83		
Controls:							
Gray matter		3.55—4.93	1.07—1.40	0.99—1.40	.79—.93	986.4	74.0—81.5
White matter		6.24—7.84	3.58—5.14	3.58—5.14	.73—.85	3706.0	64.8—73.4

autopsy (a) and after five months of storage at −15° C. (b). This may explain the difference in the hexaene levels. Otherwise, the percentages of the individual PUFA's were similar to those found on brains of patients free of central nervous system disease.[2]

Recovery and separation of the lipid fractions by chromatography, as may be seen from Table 3, were satisfactory. The data on Fraction I show that all of the highly unsaturated fatty acids participated in the esterification of the cholesterol, though their percentage distribution is different from that in the total lipids, the hexaenes being less, the dienes considerably more. Esterified cholesterol was not present in the control brain, and, therefore, no substrate for comparison was available. Wittenberg, Korey, and Swenson's[6] procedure revealed compounds with aldehydic linkage in Fraction I of gray matter, though lipid phosphorus was absent. This may be interpreted as evidence of plasmalogen cleavage with the aldehydic linkage being left intact. In none of the fractions of the control brain was there any similar finding.

In Fraction II (Table 3), which is presumed to contain the free cholesterol and the glycerides,[3] there was an admixture of negligible amounts of lipid phosphorus and plasmalogens. All the cholesterol was unesterified. The amount of fatty acids was far in excess of a 2:1 ratio for the gray matter. In the white matter, there was no lipid phosphorus and, therefore, these data suggest the presence of glycerides. In Fraction II of the white matter of the control case, a smaller amount of fatty acids was similarly present. PUFA represented approximately one-third and one-sixth of the fatty acids present in Fraction II of the gray and white matter, respectively. In the control case, they were considerably less (approximately one-fourth and one-ninth, respectively). Fraction III contained most of the phospholipids, including the plasmalogens, as anticipated.

DISCUSSION

The severe necrosis of portions of the spinal cord in the thoracic area seen in the present case is unusual. There can be little doubt from the clinical course that the spinal cord was the initial locus of involvement by the disease

TABLE 2
INDIVIDUAL PUFA IN GRAY AND WHITE MATTER (in % of Total PUFA)

		Hexaene	Pentaene	Tetraene	Triene	Diene
Patient:						
Gray matter	(a)	53.5	9.8	26.6	0	10.1
	(b)	34.6	8.8	41.2	9.3	6.1
White matter	(a)	37.4	9.0	31.8	6.9	14.9
	(b)	23.3	8.8	44.4	12.1	11.4

TABLE 3

LIPID COMPOSITION OF FRACTIONS OBTAINED BY SILICIC ACID COLUMN CHROMATOGRAPHY

	μm in total of fraction					Mg. total PUFA	PUFA in % of total PUFA				
	Lipid phosphorus	Cholesterol: Free	Cholesterol: Esterified	Fatty Acids	Plasmalogens		Hexaene	Pentaene	Tetraene	Triene	Diene
Patient:											
Gray matter:											
Charge	165.1	123.0	36.0	394.0	33.1	27.9	34.6	8.8	41.2	9.3	6.1
Fraction I	0	0	41.7	35.5	5.98	1.9	17.6	6.9	23.5	23.5	28.3
II	6.4	117.3	0	36.9	.96	3.1	28.2	8.1	43.8	11.8	8.1
III	151.6	1.4	0	292.3	22.05	19.3	3.8	22.7	52.7	16.5	4.2
Recovery in %	95.7	96.4	115.8	92.6	87.5	87.4					
White matter:											
Charge	80.6	66.0	99.9	228.5	20.39	18.2	23.3	8.8	44.4	12.1	11.4
Fraction I	0	1.6	98.7	—	.87	3.8	10.0	5.5	20.8	34.2	29.5
II	0	62.8	0	38.4	.37	1.9	17.2	9.9	51.6	16.1	5.2
III	77.4	0.1	0	155.7	15.96	10.4	32.7	7.8	49.9	5.8	3.8
Recovery in %	96.0	97.7	98.8	94.0	84.3	88					
Control:											
Gray matter:											
Charge	115.0	62.4	0	208.8	22.2	16.6	48.5	7.7	43.0	—	2.1
Fraction I	0	0	0	2.1	0				*insufficient material*		
II	16.1	66.9	0	13.4	.35	1.1	10.9	4.8	52.8	18.3	13.5
III	116.1	1.7	0	215.8	19.6	19.0	38.3	8.4	44.0	5.4	3.8
Recovery in %	115.0	110		110.8	89.8	121					
White matter:											
Charge	181.9	79.4	0	354.0	64.1	13.5	16.7	6.9	55.6	12.2	8.7
Fraction I	0	0	0	2.5	0				*insufficient material*		
II	0	75.9	0	21.3	.5	.8	11.6	5.6	60.5	22.3	0
III	171	1.2	0	313.5	60.2	12.0	12.7	7.0	60.5	12.6	7.1
Recovery in %	94.5	97.2		95.2	94.7	95.2					

process, and the presence of cystic cavitation of the cord at autopsy also strongly suggests that the process here was farther advanced than at any other part of the neuraxis. The characteristic symptom of cortical blindness then followed very shortly upon the paraplegia, and the pathologic appearance of the white matter of the occipital lobes confirms this sequence, since the damage to the myelin in this area is certainly next in order of severity of involvement to the changes seen in the spinal cord. As the disease progressed, the next clinical features to appear were mutism and dementia, and these may be correlated with the appearance of somewhat "younger" lesions extending forward through the parietotemporal and into the left frontal region. The lack of clinical involvement of cerebellum and cranial nerves is confirmed by the remarkable sparing of the cerebellum and the brain stem. The positive response to oil red o staining shows that extensive breakdown of the protein-lipid layers of the myelin had taken place. Globoid cells were not seen. This case therefore falls in the scheme proposed by Einarson and Neel[7] into their category 3: sporadic degenerative type of diffuse sclerosis with sudanophilic end products.

The chemical findings confirm the depletion of phospholipids and esterification of cholesterol, as reported by other authors[8–10] and furnish the supplementary information on the disproportionally large loss of plasmalogens in the white matter. The data on the cholesterol esterifying fatty acids reveal that PUFA participate to a lesser extent in this process than has been reported for the cholesterol esters of the liver[11,12] and of atheromatous plaques.[12,13] Higher unsaturated fatty acids (tetraene, pentaene, and hexaene), however, were found only in small amounts, or not at all, in liver or atheromatous plaques. In plasma, pentaene and hexaene are present in very small amounts. In view of the larger proportion of the highly unsaturated fatty acids in the cholesterol esters of the cerebral lesions, it is reasonable to assume that the PUFA were split from the phospholipids where they abound.[14]

The results on the lipid fractionation suggest that small amounts of glycerides are present, but it is unlikely that they alone could account for the large quantities of stainable lipids, as seen in the microscopic sections. Phospholipids in a physicochemical stage different from the normal, that is, separated from their protein linkage, must be assumed to be part of the sudanophilic lipids.

SUMMARY

1. A case of Schilder's disease is presented with a clinicopathologic discussion and chemical analysis of cerebral lipids.

2. Chemical studies revealed depletion of phospholipids and partial esterification of cholesterol. The plasmalogens of the white matter were reduced in an amount greater than other phospholipids. In the gray matter, the plasmalogens were at a level found in normal brains. Highly unsaturated fatty acids, probably split from brain phospholipids, participate in the esterification of cholesterol as well as in the formation of glycerides.

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Neurinomas of the cauda equina encountered at Djakarta

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DURING THE YEAR 1957, 4 neoplasms of the cauda equina were observed in Djakarta, all of them neurinomas. A review of our neurosurgical material for the years 1952 to 1957 inclusive revealed only 1 additional case, in 1955, and it also was a neurinoma. Since series of cauda equina tumors from outside Indonesia have indicated a preponderance of other pathologic diagnoses, a report of the clinical and pathologic findings in these 5 cases appeared to be justified.

CASE REPORTS

Case 1. A 32-year-old Indonesian man was admitted to the neurologic ward of the General Central Hospital (R.S.U.P.) in Djakarta on July 26, 1955. He gave a two-year history of low-back pain, which was aggravated by coughing and was associated with questionable weakness of the left leg.

Neurologic examination. Left straight leg raising was painful at 70°. Diminished sensation over L3 dermatome on the left and diminished left quadriceps reflex were noted. Flattened lumbar lordosis and a stiff back with tenderness to percussion over L2 and L3 spines were seen.

A partial manometric block was found at lumbar puncture, and the spinal fluid contained 780 mg. per cent protein and 7 cells per cubic millimeter, 3 of them polymorphonuclear. After lumbar puncture, quadriceps and adductor palsy developed and ascending myelography revealed a complete block at L2, apparently extramedullary. Laminectomy was performed by Drs. S. K. Handojo and S. Prawirohardjo, who removed a tumor which was firmly attached to one of the nerve roots of the cauda equina. The tumor was about 2 cm. long and 1 cm. in diameter (Fig. 1A). The pathologic diagnosis was neurinoma. Clinical recovery was almost complete.

Case 2. A 37-year-old Indonesian woman was admitted to the neurologic ward of the R.S.U.P. on June 18, 1957, complaining of increasing pain in the right lower groin and back over the previous seven years. Painful tingling and burning sensations had radiated into her legs for about two years. Urinary dribbling developed, and her legs became numb and weak, progressing to paraplegia four months before admission.

Examination. Lumbar scoliosis and tenderness of the spines of L3 and L4 were noted. Both legs were almost completely paralyzed, and the muscles involved were hypotonic. The right calf muscles were atrophic. All modalities of sensation were diminished in both legs below L1, the loss being particularly severe on the right over dermatomes L4 and 5. Deep and superficial reflexes of the legs were hypoactive or absent, and the superficial abdominal reflexes were absent in the lower quadrants.

Extensive erosion of bodies, pedicles, and laminae of L1 through L4 were demonstrated by roentgenograms. A lumbar puncture gave a few drops of clotting xanthochromic fluid.

At laminectomy, done by Drs. Handojo and Prawirohardjo, a growth 9 x 4 x 3 cm. was found (Fig. 1B) attached to a nerve root and extending from L2 to L4. The conus medul-

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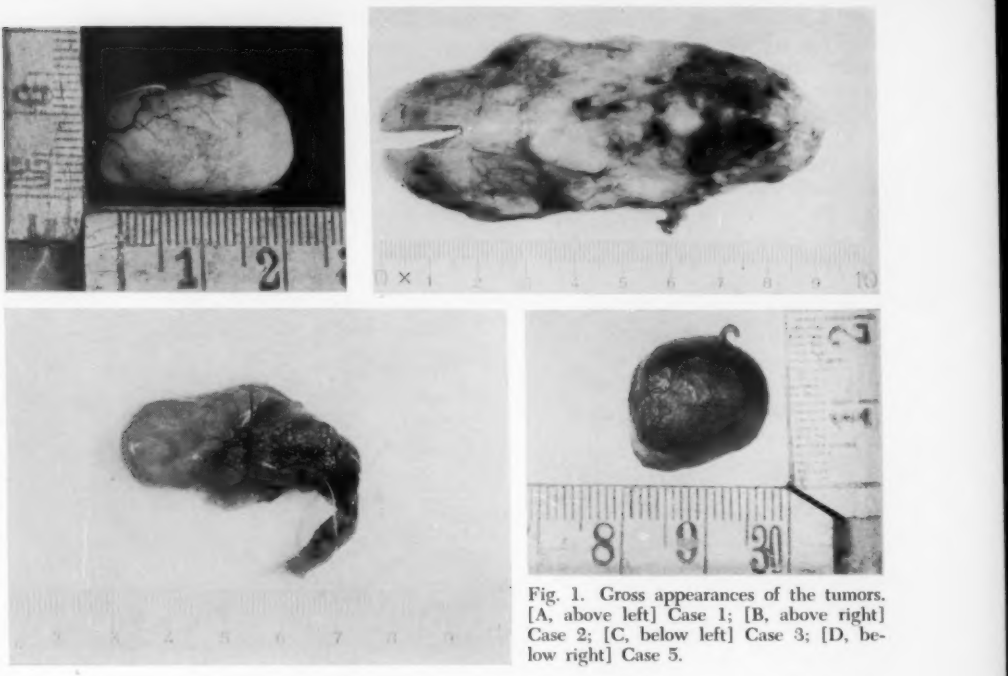

Fig. 1. Gross appearances of the tumors. [A, above left] Case 1; [B, above right] Case 2; [C, below left] Case 3; [D, below right] Case 5.

laris and cauda were atrophic. Removal was complete, and the histologic diagnosis was neurinoma. Partial return of motor power but no improvement of sensation occurred postoperatively.

Case 3. A 45-year-old Indonesian woman was admitted on August 6, 1957, giving a history of intermittent pain in the low back and right pelvis. One year before admission, her right leg began to feel numb with disagreeable dysesthesias. Right leg weakness began three months before admission, and the left leg became involved a few weeks later.

Lumbar scoliosis, fixation of lumbar movement, and tenderness to spinal percussion were found. Complete paralysis of distal muscles of the right leg and considerable paresis of the left leg, again more severe distally, were noted. The patient had hypesthesias, hypalgesia, and some hyperpathia of both legs, more marked on the right. No triceps surae reflex was elicited on the right. That on the left was hypoactive, as were both quadriceps reflexes. The right plantar response was abnormal. Sphincter ani and abdominal reflexes were impaired.

Roentgenograms showed atrophy of the pedicles of D12, L1, and L2, with widening of the interpedicular distances. At lumbar puncture, xanthochromic clotting spinal fluid was obtained, with 1,360 mg. per cent protein. Ascending myelography revealed a block at the D12-L1 interspace.

Laminectomy by Dr. S. Prawirohardjo disclosed an extramedullary tumor 6 x 2 x 1.5 cm. (Fig. 1C), extending from D11 to L1. Atrophy of the cord and cauda was distinct. The tumor was adherent to a nerve root but was extirpated in toto. Neuropathologic diagnosis was cystic neurinoma. Very little improvement was experienced postoperatively.

Case 4. A 26-year-old Indonesian woman was admitted to the neurologic ward on September 13, 1957. For a year, she had had

dull lumbosacral pain extending into both legs, which was followed by weakness of the legs and urinary incontinence three months before admission.

Pain on straight leg raising at 70° on the left and paraparesis, left worse than right, were noted. Some atrophy of left calf and foot musculature was found. Sensation was diminished, left more than right. Muscle stretch reflexes were diminished, especially on the left, but abdominal skin reflexes were normal.

On roentgenograms there was distinct erosion of L3 to 5 bodies and atrophy of the adjacent pedicles.

Total manometric block was found on lumbar puncture. Xanthochromic fluid was obtained, which quickly clotted. Protein content was 920 mg. per cent.

At laminectomy, a pencil-sized growth was found extending from L2 to L5, apparently originating in and compressing the left side of the cauda equina. Removal was difficult because of the tumor's soft consistency. Histologically, it proved to be a neurinoma (Fig. 2).

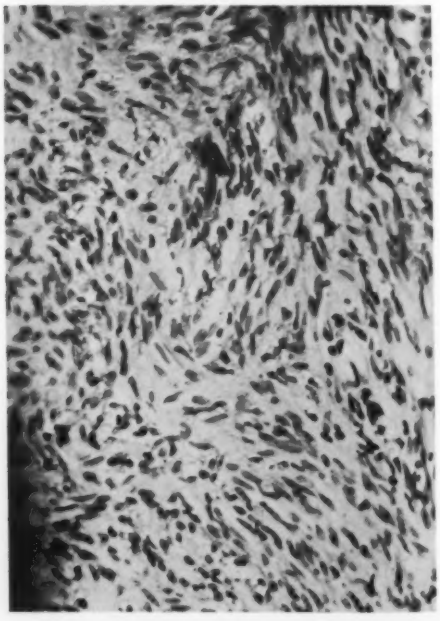

Fig. 2. Histologic appearance of tumor in Case 4. Note parallel arrangement of spindle-like cells and tendency for palisading. See text for further details.

Recovery was gratifying. The patient's sensation improved somewhat; she was able to walk unsupported seven weeks after operation, and bladder control returned almost to normal.

Case 5. A 47-year-old Indonesian-Chinese man was admitted to the Tjikini Hospital, Djakarta, on December 20, 1957, complaining of dull pain in the back and upper left leg for three years. The pain was aggravated by sneezing, coughing, or straining, at which times it radiated down to the left knee.

The patient stood in a stooped posture and refused to straighten up because of pain. He had tenderness over L1 to 3 and flattened lumbar lordosis. The straight left leg could be raised only 30°, and raising the right leg beyond 70° also caused left leg pain. Mild loss of sensation was noted over dermatome L5 on the left.

Lumbar spine films were normal. Spinal fluid was slightly xanthochromic, with 248 mg. per cent protein. There was a questionable manometric block, and partial anatomic block was demonstrated at L2-3 disk by myelography. Although the myelogram had the characteristics of a disk, it was felt clinically that a tumor was more likely. Actually, both were found.

Hemilaminectomy was done at L3 with removal of an extradural mass of ruptured disk material, after which signs of a combined conus and cauda equina lesion appeared. Repeat myelography showed a total block at L1, and a second laminectomy revealed a neurinoma which had compressed the conus. The tumor measured 1.5 x 1 x 1 cm. (Fig. 1D).

Recovery was incomplete. Some dribbling of urine remained, but bladder control improved and the leg pain disappeared. Muscles of the left calf and foot became atrophic postoperatively.

DISCUSSION

In the years 1952 to 1957 inclusive, 5 tumors of the cauda equina were observed in Djakarta. All the growths showed the histologic features of neurinomas. None of the

patients had findings to justify a diagnosis of multiple neurofibromatosis of von Recklinghausen. During the same period, 24 primary intraspinal tumors at higher levels of the cord and 164 primary intracranial neoplasms were observed.

A review of the literature disclosed only 9 previously reported cases of intraspinal tumors in Indonesia.[1–6] The only one of these which was located in the cauda equina was the second case of van Wulfften Palthe.[5] It was a neurinoma.

This histopathologic invariability is in striking contrast to generally reported experience,[7–10] gliomas and vascular growths being found in the cauda equina in addition to neurinomas. In Guillain's series[9] of 7 cauda growths, gliomas preponderated, there being only 2 neurinomas.

Grossly, the tumor in the present Case 4 suggested a glioma; however, the parallel arrangement of long spindle cells with palisading of nuclei left little question that this tumor also was a neurinoma (Fig. 2).

In the present series, 3 of the neurinomas were of the size described as "giant tumors" by Elsberg.[7] However, the duration of clinical findings did not differ from that in patients with smaller growths, suggesting a more rapid growth of the larger tumors. No histologic differences were seen which could be correlated with this difference in size, nor was there histologic evidence of sarcomatous degeneration in any of the 5 tumors.

SUMMARY

In the years 1952 to 1957 inclusive, 5 tumors of the cauda equina were encountered at Djakarta. All these neoplasms were histologically neurinomas.

A review of the literature has revealed only 1 other tumor of the cauda equina previously reported in Indonesia, and it also was a neurinoma.

This incidence of neurinomas contrasts sharply with observations of workers outside Indonesia.

The authors wish to thank the staff of the Institute of Pathology, University of Indonesia Medical Faculty (Head: Sutomo Tjokronegoro), and the staff of the Neurosurgical Clinic of the Central General Hospital in Djakarta (Head: S. K. Handojo), who made available the material used in this report. Dr. Bill Garoutte of the University of California Medical Center, San Francisco, kindly read and commented on the manuscript.

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Temporal lobe epilepsy resulting from ganglioglioma

Report of an unusual case in an adolescent boy

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THIS CASE concerns a boy with a four-year history of temporal lobe seizures who died accidentally by drowning. Except for the seizures, he was neurologically normal but responded poorly to treatment. On autopsy, a tumor was found in the left temporal lobe. Children with seizures resistive to treatment should be carefully studied before long range therapy is started.

HISTORY

R. H., age 17, was examined by one of us (A.T.S.) in February 1954. Transitory peculiarities in behavior beginning at the age of 13 were discounted by the parents until the boy was 15 years of age, when they were recognized as significant.

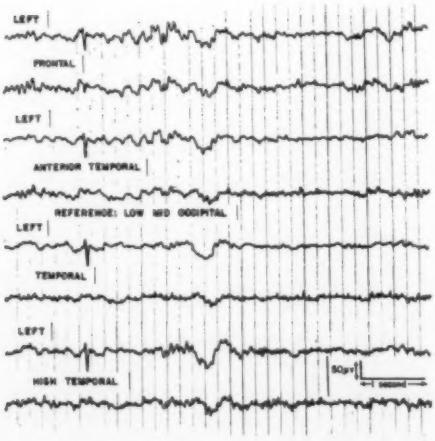

Fig. 1. Electroencephalogram (March 8, 1954)—left frontotemporal spikes and slow waves

Description of seizures. His seizures were of the temporal lobe variety and were characterized by an auditory aura described as "ringing or buzzing sound" or a "feeling" that he could hear familiar expressions experienced previously in a dream. Some attacks began with a sound of "dogs barking across the street." At times, the aura was described as a "vision" of a scene or a memory previously experienced. At other times, he described a new scene which seemed to have appeared previously. On some occasions, a picture on the wall appeared to be unusually vivid. Automatisms accompanied these spells, during which he would arrange things on tables, eat automatically, draw automatically, or deliver newspapers without making errors but also without remembering what he had done. In some spells, he would whistle or play records and whistle to the music. In other spells, words repeated over and over again seemed to have been heard previously. Again he would feel that he was doing things over and over again. Some spells resembled panoramic memory. Both familiar and unfamiliar feelings accompanied the visual phenomena. The seizures had no olfactory or gustatory components, but occasionally he was observed to sweat during a spell. He always had complete amnesia during the attacks. The spells lasted from ten seconds to thirty minutes and varied in frequency from a few spells a month to as many as 18 in a week. After January 1955, they averaged 6 or 7 per month, most of which occurred in the morning hours.

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The past medical history was irrelevant. A 14-year-old paternal cousin had "convulsions" and the maternal grandfather died with a "brain tumor."

Physical examination. The general medical examination and the neurologic examination were completely normal, but an electroencephalogram made March 8, 1954, showed in the wake record dominant, low-amplitude, 9- to 10-per-second alpha rhythm. With drowsiness, inconspicuous slow irregularities and small sharp spikes appeared in the left hemisphere anteriorly (Fig. 1). Dr. E. H. Trowbridge, Jr., who had treated the boy previously, interpreted the electroencephalogram as consistent with a temporal lobe type of dysrhythmia. He recommended pneumoencephalogram, but the boy's family refused to let him carry out the procedure.

In summary, the seizures over a four-year period in this boy were characterized by peculiar psychic and dream-like experiences accompanied by automatisms and amnesia. Both auditory and visual hallucinations and illusions occurred as prodromals. There were no gustatory and olfactory components, lip movements, swallowing automatisms, or grand mal seizures.

Between February 1954 and July 1955, the patient was treated by one of us (A.T.S.) with many anticonvulsant drugs which did not appreciably control the seizures. Hospital study was again postponed by the parents. On July 7, 1955, the patient drowned while swimming under water, perhaps as the result of a seizure. All attempts at resuscitation failed. An autopsy was performed under the direction of Dr. F. C. Helwig, pathologist, who kindly permitted us to study the brain.

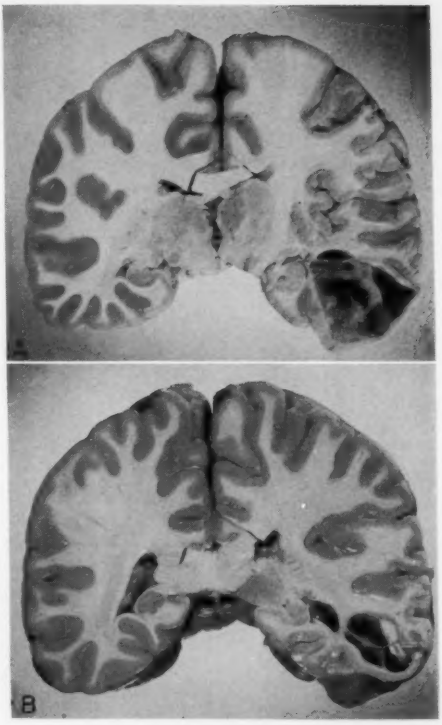

Fig. 2. Coronal section of gross brain. [A] Level of largest diameter of tumor in left third temporal convolution. [B] Cystic cavitation by tumor lying posterior to solid mass

PATHOLOGIC EXAMINATION

Gross. The brain appeared normal and weighed 1,660 gm. There was slight widening of the left third temporal convolution. A well circumscribed cystic tumor was found in the left third temporal convolution, lying subcortically, approaching the gray matter along the crown of the convolution in the area shown in Figure 2A. The tumor measured 3 x 2.5 cm. at its largest diameter, 4.5 cm. posterior to the left temporal pole. Figure 2 shows the solid portion of the tumor surrounded by cystic areas and demonstrates the relationship to the position of the hippocampal gyrus and the fusiform gyrus as well as the rest of the adjacent temporal convolutions. The tumor was gray in color, with areas of brown discoloration, and very cystic and cut with increased resistance. Multiloculated cysts occupied the white matter adjacent to the tumor except medially and inferiorly (Figs. 2 and 3). The cystic cavities extended caudally to the level of the pulvinar.

Microscopic. Representative areas of the brain and tumor were stained for numerous tissue elements by standard methods. Except for some swelling and pallor of the glial cells, no abnormalities were noted. Changes were found in the areas adjacent to the tumor. Here,

there was pallor of the myelin sheaths along the edge of the tumor (Fig. 3A). Thionine stains showed that the tumor was entirely subcortical except near the crown of the convolutions (Fig. 3B). The tumor mass had not invaded the ventricle, and all the cystic cavities were subcortical. All but one of the cystic cavities within the tumor were small (Fig. 3). Where the tumor approached the cerebral cortex (Fig. 3B), reactive gliosis merged with the large pale astrocytic nuclei forming part of the tumor. The nerve cells of the lower layers of the cerebral cortex showed chromatolysis, shrinkage, and liquefaction necrosis. In general appearance, the tumor was not very cellular; the background was fibrous with dense strands collected in bunches in some areas. This varied because of numerous cystic cavities and because of areas of degeneration (Fig. 4A). Many tumor cells were arranged in multinucleated clumps. The size and shape of the nuclei varied, as did the amount of cytoplasm in the cells. Amorphous material occupied the larger cysts (Fig. 4C), but some of the smaller cavities were lined by dark hyperchromatic nuclei which resembled lymphocytes but probably were tumor cells. One area of the tumor showed angiomatous changes, and in general the tumor was avascular. The degenerative areas showed clumps of eosinophilic staining material, some of which appeared to represent degenerated glial fibers which stained deep red in Gomori's trichrome stain and were considered Rosenthal fibers (Fig. 4C, arrow). Phosphotungstic acid hematoxylin stains showed abundance of glial fibers (Fig. 4B), and Cajal gold sublimate stains demonstrated large fiber-building astrocytes (Fig. 4D) but also spongioblastic elements. No mitotic figures were seen; 3 to 8 nerve cells appeared in each high-power field (Fig. 5A, arrow) and showed large nucleoli and Nissl granules (Fig. 5D, left). Some of these cells contained 2 and possibly 3 nuclei (Fig. 5D, upper right). The nerve cells contained axis cylinders demonstrable in Bielschowsky and Cajal reduced silver methods (Fig. 5E). The nerve cells varied in size from large pyramidal cells to smaller cells more fusiform and pear-shaped. Some of them showed chromatolysis and cytoplasmic disintegration.

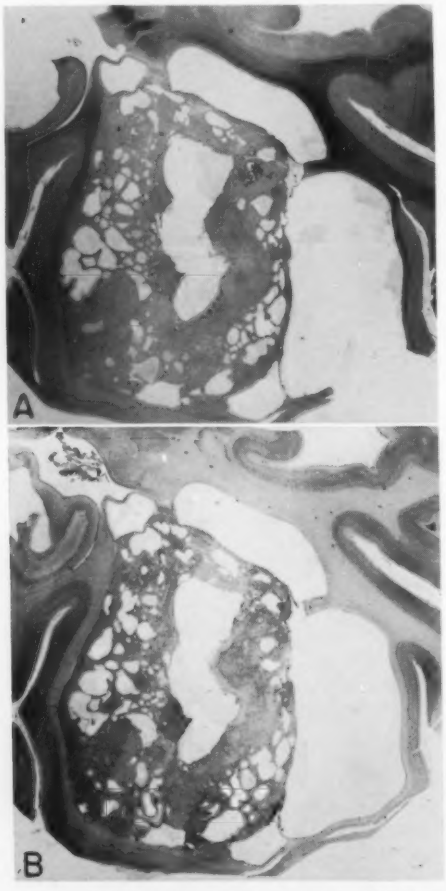

Fig. 3. Photomicrograph of tumor and left third temporal convolution. Enlarged from x 3. [A] Myelin sheath stain (Loyez method). [B] Nissl stain, same magnification

The angiomatous malformation lying in the right superior aspect of the tumor shown in Figure 3A consisted of large vascular spaces filled with red blood cells. Some had only a single endothelial layer for a wall, while others had thicker walls (Fig. 5B, arrow), which show accumulations of compound granular phagocytes (Fig. 5C, center). The phagocytic cells contained iron pigment (Fig. 5B and C), and similar accumulations of pigmented material could be seen in the wall of the degenerated zones as well as around the vascular spaces (Fig. 5B, X).

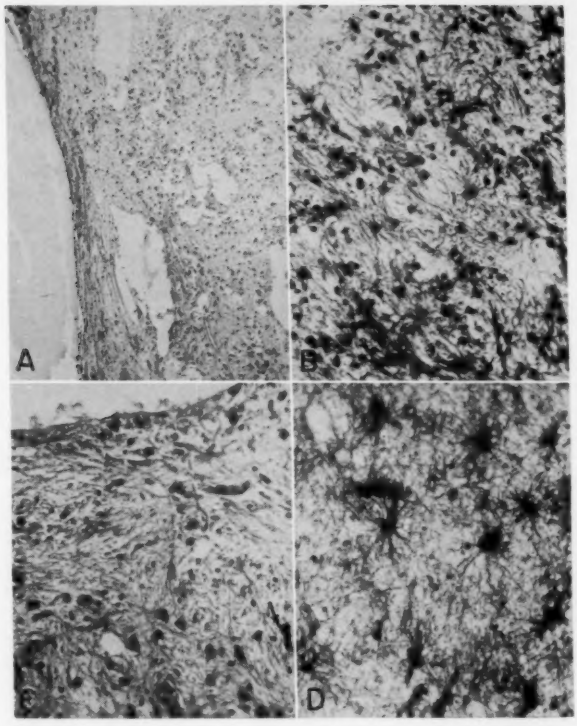

Fig. 4. Histology of tumor. [A] Large cyst, left. Note cystic changes and degree of cellularity. Hematoxylin and eosin stain. x 60. [B] Glial fibrils. Note nuclear forms. Phosphotungstic acid hematoxylin stain. x 235. [C] Fibrillary and nuclear appearance near cyst wall above. Eosinophilic globules near cyst wall. Rosenthal fiber (arrow) hematoxylin and eosin stain. x 235. [D] Large tumor astrocytes. Note smaller nuclei. Gold sublimate stain. x 235

DISCUSSION

Pathologically, this tumor belongs to a controversial group. The angiomatous malformation suggests that the patient had a congenital hamartoma in the temporal lobe which probably underwent malignant transformation. The neoplasm is mostly a cystic astrocytoma but also contains other glial elements. The nerve cells scattered throughout the tumor seem to be an intrinsic part of it but may have initially been part of a heterotopic nodule or part of a hamartoma. Otherwise, the tumor resembles a cystic astrocytoma with degenerative changes. Because the gliomatous portion of the neoplasm is not exclusively astrocytic, we prefer to classify the growth by the term ganglioglioma. Some authors[1] believe tumors of this variety undergo malignant change by proliferation of the glial and not the neuronal elements.

Clinically and pathologically, this tumor is benign. Rosenthal fibers seen in spongioblastomas[2] occur also in ependymomas and hemangioblastomas.[3] Histochemical studies suggest they may arise from degeneration of subependymal glial elements.[4] It has been suggested that subependymal glial tumors containing Rosenthal fibers and arising in the temporal lobe may be of congenital origin.[3] The long history of seizures of unchanged character also point to slow growth. A subependymal site of origin is further suggested because the tumor would probably not cause seizures until the gray matter at the base of the third temporal convolution is invaded. Most of the 8 small temporal lobe tumors associated with psychomotor epilepsy reported by Cavanagh[5] were considered to have arisen in childhood and were classified as hamartomatas. A few showed neoplastic transformation, but none resembled the tumor reported here. Penfield and Jasper[6] found that seizures as an initial symptom oc-

curred most often with slow-growing tumors. Of 230 verified supratentorial gliomas, 64 were classified as more benign astrocytomas; 70% of those with astrocytomas had seizures.

Hamartomas are defined by Greenfield and associates[7] as "congenital malformations with a potentiality for growth that does not exceed that of the normal tissue in which they are situated." Zülch[2] prefers the term "hamartoblastoma" for those with autonomous growth. He objects to the classification of some tumors by the term "gangliocytoma" and classifies these tumors into a separate group of neuroepithelial tumors that have different biologic characteristics depending on their location. Tönnis and Zülch[8] describe some ganglion cell tumors of cystic character occupying the mediobasal temporal lobe. These occur in young persons and are relatively benign. Kernohan[9] considers all gangliocytomas as "neuroastrocytomas," which he classifies into 4 grades of malignancy. Zülch rejects this classification. In a recent report,[10] some harmartomas found in the posterior hypothalamus were associated with precocious puberty. The authors make a distinction between hamartomas, which they define as "heterotopic hyperplastic malformations," and gangliogliomas, which they consider a "dysontogenic," that is, an embryonal defect. Because of the controversy regarding tumors classified as "gangliocytomas," we prefer to use the term "ganglioglioma" for the tumor described here because of its histologic characteristics. Biologically, the tumor was benign and the prognosis probably would have been good if it had been surgically removed.

In the clinical consideration of this case, we prefer the diagnostic label "temporal lobe epilepsy" rather than the current popular term "psychomotor epilepsy." The classification of temporal lobe seizures is still controversial.[11] Clinically, this patient showed the type of seizures described by Hughlings Jackson[12] as nonconvulsive epileptic seizures characterized "by exceedingly complex purposive seeming action." Intricate psychosensory phenomena were an essential part of the seizure. The latter component, or "dreamy state," was observed by Jackson and identified at autopsy with lesions in the temporal lobe. Because of

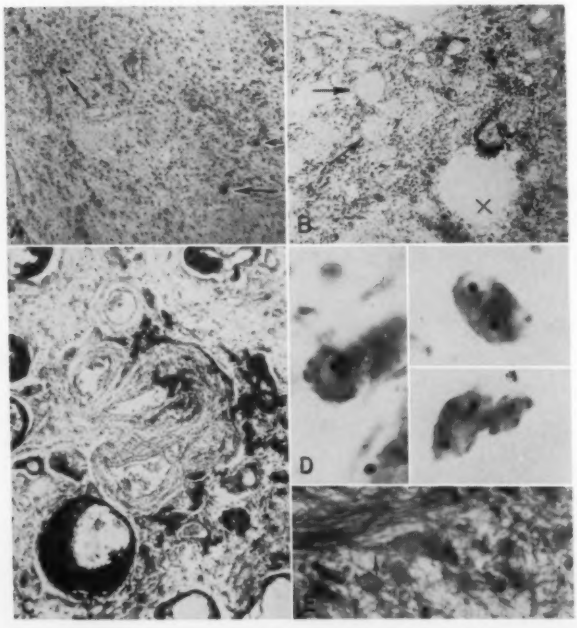

Fig. 5. [A] Denser area of tumor. Nerve cells indicated by arrows. Nissl stain. x 60. [B] Thin-walled vascular channels (arrows). Cystic cavity at x. Pigmented phagocytes around vascular channel upper edge of x. Nissl stain. x 60. [C] Angiomatous malformation. Thin-walled vascular channels surrounded by adventitia which is packed with phagocytic cells (foam cells). Bielschowsky stain. x 60. [D] Nerve cells in tumor. Cell at left has distinct Nissl granules. Cell right above has 2 well developed nuclei and a third poorly developed nucleus. Cell right below has 2 nuclei but some degeneration and finely granular Nissl substance. Nissl stain. Enlarged 2 diameters from x 375. [E] Nerve cell. Neurofibrillae visible in process (arrow). Cajal reduced silver stain. x 375

the uncinate component in seizures of this type, he used the expression "uncinate fits" but never sharply delineated what he meant by the uncinate region.[11] The term "psychomotor epilepsy" introduced later[13] was accompanied by automatisms and showed 6-per-second, flat-topped waves mixed with rhythmic sharp waves in the electroencephalogram. Gastaut[14] prefers the term "partial epilepsy" for seizures that include the types described as temporal lobe seizures. Wilson[15] described such seizures as "epileptic variants." Objections have been made[11, 16] to attempts to define and correlate a complex clinical seizure disorder with an electrophysiologic pattern. It is doubtful if the term "temporal lobe epilepsy" will replace the term "psychomotor epilepsy" which now seems well established in clinical parlance. In this case, however, a single lesion was found in a small area in the third temporal convolution. For that reason, we prefer the diagnosis "temporal lobe epilepsy."

The etiology of temporal lobe seizures in children is more often induced by degenerative and inflammatory lesions than by tumors. This can be explained by the higher incidence of brain tumors in the posterior fossa before the age of 15. In 157 cases of temporal lobe seizures, Earle, Baldwin, and Penfield[17] found 100 cases of pathologic changes apparently caused by compression or by anoxia at the time of birth. In the remaining 57 cases, there was evidence in the temporal lobe of postnatal injury, intracranial infection, and neoplasm. In their total series of 2,484 cases of epilepsy, Gibbs and Gibbs[18] found 121 cases had been operated for temporal lobe tumors. This incidence would naturally not be expected in children. Bingley[11] recorded 16 gliomas in 190 cases of temporal lobe epilepsy. It is very difficult to correlate the site of a lesion with the pattern of a convulsive seizure, particularly in tumor cases. This may be because the lesion is not discrete or because the size is extensive at the time of death. The present case is unusual because neither of the above objections apply, and, if it can be assumed that the lesion alone was responsible for the seizures, it must have been a clinically active lesion for at least four years, yet one of relatively small size. At the time of death, there were no organic neurologic signs and no evidence of increased intracranial pressure. Only the cystic cavities adjacent to the tumor extended into the middle and posterior regions of the third temporal convolution, and these were limited to subcortical white matter. Therefore, it may be assumed that the discharging focus arose in the cerebral cortex of T3, where the tumor approached the gray matter. The clinical manifestation may represent psychic and motor phenomena resulting from the spread of this abnormality into other temporal areas.

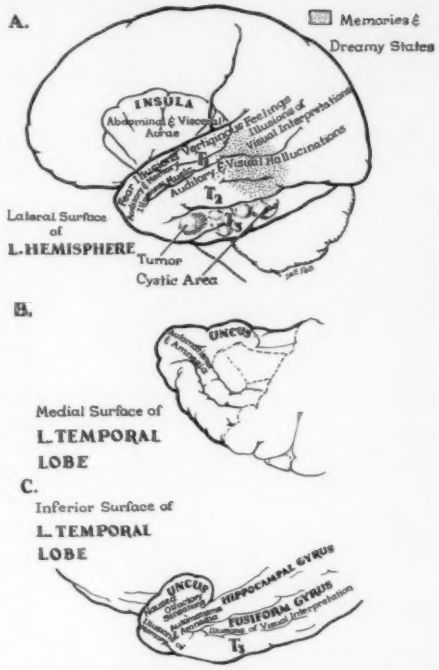

Fig. 6. Schematic drawing to show responses obtained by electrical stimulation of the temporal lobe in man (modified after Penfield). [A] Left lateral view. Note position of tumor. [B] Medial surface of temporal lobe. [C] Inferior surface of temporal lobe

The seizure pattern in this case can be divided into 5 components: [1] altered consciousness, [2] automatism, [3] visual and auditory sensory phenomena, [4] complex psychic states, and [5] visceral components. Sweating, which occurred at times in this pa-

tient, represents a visceral discharge but seems to be unusual with temporal lobe epilepsy.

It cannot be said with certainty how or where a discharging lesion projects. Penfield and his associates[6, 19, 20] have demonstrated that electrical stimulation induces symptoms in epileptic patients identical with those experienced during their seizures. The schematic drawing in Figure 6 shows the position of the tumor in our case and the general types of epileptic phenomena found by Penfield and associates from stimulation experiments on the human brain. Although these responses overlapped, most of the responses were concentrated around the temporal pole and the upper temporal convolutions. In their drawings, these authors did not show many responses from the third temporal convolution. In this case, let us assume that epileptic discharge arises in the cerebral cortex overlying the tumor and produces the epileptic phenomena described by spreading into other areas of the temporal lobe (which may correspond to the zones discovered by electrical stimulation of the cerebral cortex); the spread would apparently activate the fusiform gyrus, temporal pole, and the first and second temporal convolutions but probably not the uncus. It might be argued that electrical stimulation of the cortex does not indicate exactly where the psychic components are activated, but at the present time there seems to be no other type of data that would offer a better correlation. Penfield[19, 20] considers the anterior portion of the temporal lobe lying lateral to the uncus as the "interpretive cortex," which, when stimulated, is capable of reproducing many of the phenomena seen in Jackson's "dreamy states." Penfield classified many of these responses as "interpretive" and "experiential." Whenever possible, such symptoms should be correlated with discrete pathologic lesions. In the case reported here, we have attempted this type of clinical-pathologic correlation.

SUMMARY

1. A case is reported of a 17-year-old boy with convulsive seizures of four years' duration. The seizures were characterized by peculiar psychic and dream-like experiences accompanied by automatisms and amnesia. Visual and auditory hallucinations and illusions initiated the seizures, but there was never any grand mal type of convulsions.

2. Death occurred accidentally by drowning. At autopsy, a small tumor, classified as ganglioglioma, was found in the left third temporal convolution. The pathology and classification of the tumor are discussed.

3. Correlation of the site of the tumor with the clinical symptomatology is presented.

We are deeply indebted to Dr. Harry Zimmerman of New York City for his observations and suggestions regarding the interpretation of histologic elements in the tumor.

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The electroencephalogram in cases of benign intracranial hypertension

Alvin D. Sidell, M.D., and David D. Daly, M.D.

Electroencephalographers have paid relatively little attention to the effects of simple intracranial hypertension on the electroencephalogram, having been more concerned with alterations in electric activity resulting from lesions which, in turn, may cause intracranial hypertension. In an early study, Williams[1] concluded that there was no correlation between abnormality in the electroencephalogram and the pressure of the cerebrospinal fluid. However, in his study, he considered a group of cases, including supratentorial and infratentorial tumors, in which the processes leading to intracranial hypertension were not the same in all instances.

Stewart,[2] in an experimental study, recognized the need for distinguishing the mechanisms by which intracranial hypertension developed. He injected lamp black into the cisterna magna of kittens producing "active" hydrocephalus, which developed on the ninth day after injection and was associated with large slow waves in the electroencephalogram. Stewart termed this type of intracranial hypertension "increased intraventricular pressure." In contrast to this obstructive hydrocephalus, he caused so-called generalized intracranial pressure by application of hydrostatic pressure to the foramen magnum, intravenous injection of distilled water, or ligation of veins draining the cranium. In both the acute and the chronic form of generalized intracranial pressure, the electroencephalogram was unchanged. He concluded that generalized engorgement or edema of the brain did not alter its normal electric activity.

Stewart also commented on 3 patients with "meningeal hydrops" who had papilledema but no hydrocephalus. The electroencephalograms of all 3 patients were normal. His study was of great practical importance since it emphasized that the process leading to intracranial hypertension determined the occurrence of an abnormality in the electroencephalogram, an abnormality which appears only in the presence of increased intraventricular pressure. Confirmation of Stewart's observations concerning generalized intracranial pressure came from Forster and Nims;[3] these authors showed that, in animals under anesthesia, rapid increase of the intracranial pressure by hydrostatic means did not cause change in the electroencephalogram until the pressure of the cerebrospinal fluid exceeded the blood pressure, at which time the brain waves disappeared.

Subsequently, in a study of rhythmic slow discharges in the electroencephalogram, Cobb[4] cast some doubt on the clinical validity of Stewart's observations. Cobb expressed the opinion that rhythmic delta discharges were associated with lesions located in the epithalamic region, but he added, "No correlation is found with raised intracranial pressure or internal hydrocephalus."

In a study of 87 patients with tumors of the third ventricle and posterior fossa or nonneoplastic obstructive hydrocephalus, Daly and associates[5] concluded that one factor determining the presence of bisynchronous rhythmic slow discharges in the electroencephalogram was the development of hypertension within the third ventricle. Other modifying factors appeared to be the rapidity of rise of intracranial pressure and the age of the patient. The hypothesis was offered that pressure on midline thalamic structures caused a disturb-

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ance in the diffuse projection system and gave rise to generalized electric abnormality. These findings support the experimental observations of Stewart[2] regarding the effects of increased intraventricular pressure.

In 1955, Foley[6] reviewed extensively the clinical aspects of cases of benign intracranial hypertension. He commented briefly that, if instances of increased intracranial pressure due to thrombosis of a major lateral sinus were excluded, the remaining cases of benign intracranial hypertension did not show significant abnormality in the electroencephalogram. Subsequently, authors writing on pseudotumor cerebri have made only passing reference to electroencephalography. Davidoff[7] remarked, "A majority of them [patients with pseudotumor cerebri] showed electrical recordings interpreted as within normal limits." He added that 5 patients who had abnormal records "belonged to the group in which infection or trauma preceded the onset of the illness." Sahs and Joynt[8] mentioned that electroencephalograms of 3 of 4 patients with pseudotumor cerebri were normal. The electroencephalogram of the fourth patient was abnormal; however, this case was atypical in that the patient was subject to convulsions. Because of the paucity of reports of electroencephalographic examinations in such patients, we felt it desirable to review the electroencephalograms in a series of patients in whom the diagnosis of benign intracranial hypertension seemed well founded.

We examined the records of the electroencephalographic laboratory at the Mayo Clinic from 1946 to the present and reviewed all cases in which a clinical diagnosis of pseudotumor cerebri or benign intracranial hypertension had been made. From these, a series of 16 cases was selected. We accepted only patients who showed papilledema but no other symptoms or signs of focal disease of the nervous system. In all patients, ventriculography, pneumoencephalography, or both revealed ventricles of normal size with no displacement from their normal position. These criteria conform to those defined by Foley.[6]

ELECTROENCEPHALOGRAPHIC TECHNICS

Routinely, 14 electrodes were applied by using a parasagittal line of 5 electrodes on both right and left sides, together with 1 electrode on each side in the region of the fissure of Sylvius and 1 electrode on each ear. Recordings were made with both scalp-to-scalp and scalp-to-ear derivations. All examinations were made while the patients were awake and resting quietly with their eyes closed. If the patients were able to cooperate, they were asked to open their eyes for about fifteen seconds in the course of each standard run in the recording. They also were requested to induce hyperventilation for three minutes at the end of the recording.

OBSERVATIONS

Data regarding these patients are summarized in the table. The ages ranged from 5 to 57 years, with the peak incidence being in the fourth decade. As has been observed by most authors, women outnumbered men. Our series included only 2 males, and, in 1 (Case 15), intracranial hypertension followed cerebral trauma. Obesity occurred with striking frequency among these patients. Exclusive of children, 10 of 13 patients were exceedingly obese.

With regard to the electroencephalograms, the recordings of 11 patients were within normal limits. In 5 patients (Cases 4, 5, 8, 14, and 15), 4- to 7-cps theta activity was recorded. In Case 4, infrequent bursts appeared in electrode derivations from the temporal regions. In Case 14, 1 burst of diffuse, bilaterally synchronous discharges of 6 cps occurred. This lasted less than one second and was the only burst which occurred throughout the recording, even during hyperventilation. In Case 5, theta activity was recorded from electrodes in the temporal region. This finding is of uncertain significance because of the child's age (9 years) and the known variability in maturation of brain rhythms in children. In Case 15, occasional bursts of theta rhythms appeared in temporal electrode derivations. Although theta rhythms can occur in the recordings of adolescent children, this boy's record seemed to us to show excessive theta activity. In Case 8, the recording made with the patient in the resting state showed brief but recurrent bursts of diffuse bilaterally synchronous theta rhythms. The duration of the bursts increased strikingly during hyperventilation and persisted for an

PERTINENT CLINICAL AND ELECTROENCEPHALOGRAPHIC DATA

Case	Age, years	Sex	Height, inches	Weight, pounds	Duration, years	Symptoms: Headache	Symptoms: Visual blurring	Symptoms: Vomiting	Papilledema, diopters	Cerebrospinal fluid: Cells*	Cerebrospinal fluid: Protein†	EEG	Remarks
1	29	F	63	157	2/12	+	+	–	4	1 L‡	10	Normal	Well in 6 months
2	8	F	—	—	1/12	+	Diplopia	+	5	2 L	30	Normal	Negative exploration; well 1 month and 12 years later
3	48	F	63	180	1	+	+	–	2	11 L	10	Normal	
4	29	F	62	174	4/12	+	–	–	R:3; L:4	—	—	Theta	Well in 6 months
5	9	F	—	—	1/12	+	+	+	2	6 L	15	Theta	Palsy right sixth nerve; well in 2 months
6	48	F	62	217	1½	+	+	–	4	1 L	10	Normal	Well in 2 years
7	37	F	68	150	?	–	–	–	6	7 L; 12 P§	10	Normal	Negative exploration; well in 3 years
8	31	F	63	173	3½	+	+	–	R:1; L:3	1 L	10	Theta	
9	19	F	60	200	1/12	+	+	+	5	11 L	40	Normal	Well in 9 months; residual pallor
10	5	F	—	—	?	–	–	–	2	0	100	Normal	No symptoms; choke found on examination; better in 3 months
11	32	M	69	210	2/12	–	–	–	2	Bloody	—	Normal	
12	16	F	63	107	1/12	+	Diplopia	–	2	Bloody	35	Normal	Palsy right sixth nerve
13	30	F	62	192	3/12	–	+	–	6	6 L	30	Normal	
14	37	F	61	183	3/12	+	–	–	R:4; L:1	5 L	45	Theta	Well in 3 months
15	16	M	—	—	2/12	–	–	–	R:2; L:1	3 L	25	Theta	Post-traumatic
16	48	F	63	147	5	–	+	–	R:2; L:3	1 L	35	Normal	

*Per cubic millimeter of fluid
†Milligrams per 100 cc. of fluid
‡Lymphocytes
§Polymorphonuclears

unusually long time after the cessation of overbreathing. We interpreted this record as abnormal.

REPORT OF CASE

The following case is typical for patients in our study.

Case 13. A 30-year-old married woman registered at the Mayo Clinic in December 1956 because of difficulty with vision. For the preceding six months, before falling asleep at night, she would hear a roaring noise which resembled the sound heard when a sea shell is placed against the ear. Three months later, she observed that, if she bent over, her vision became blurred. After one month, this blurring became more persistent, and she had difficulty in reading the newspaper or watching television. She finally consulted her home physician, who found that she had papilledema and referred her to the clinic for further studies. She denied headache or other symptoms suggestive of increased intracranial pressure.

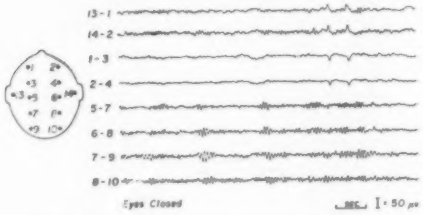

Fig. 1. Electroencephalogram, Case 13

Fig. 2. Pneumoencephalogram, Case 13. Note normal size of lateral and third ventricles in posteroanterior view.

The patient was 62 in. tall and weighed 192 lb. Visual acuity in both eyes was normal. There was bilateral choking of the optic disks with the right disk elevated 5 diopters and the left 6. Examination of the visual fields revealed enlargement of both physiologic blind spots. The remainder of the neurologic examination disclosed normal findings.

Urinalysis gave normal values as did estimations of the hemoglobin, leukocyte count, and erythrocyte sedimentation rate. Roentgenograms of the skull did not disclose evidence of abnormality, and an electroencephalogram (Fig. 1) did not show abnormal discharges.

On January 3, 1957, ventriculography was performed; however, insufficient air entered the ventricles for adequate examination. A pneumoencephalogram was then made (Fig. 2) and revealed the ventricles to be of normal size and in normal position. Spinal fluid obtained at the time of ventriculography contained 6 lymphocytes per cubic millimeter and a total protein of 30 mg. per 100 cc.

At the time of dismissal, the patient was placed on a reduction diet and advised to restrict her intake of sodium and water. She was seen again on February 26, 1957, at which time the papilledema was unchanged; however, she had lost 20 lb. in the intervening two months. By March 25, 1957, she had lost 25 lb. On examination, the elevation of the optic disks showed a decrease to about 3½ to 4 diopters, and the venous congestion had subsided, so that spontaneous pulsations were visible in the disks. By May 20, 1957, she had lost 30 lb.; the papilledema, however, had not decreased further. A letter from her home physician in January 1958 stated that she still had papilledema of about 4 diopters but that her visual acuity was normal. Her physician reported recently that she had not returned for further examination but apparently was well.

COMMENT

In this series, the high incidence of normal electroencephalograms is in marked contrast with the findings observed in patients who have increased intracranial pressure due to obstructive hydrocephalus. We have already referred to our study[5] of 87 patients with obstructive hydrocephalus; 63 of these patients had papilledema, and electroencephalograms for 53 (84%) of the 63 showed evidence of abnormalities. Conversely, in the present study, the majority of patients had normal electroencephalograms. The tracings of Cases 4 and

14 showed meager amounts of theta rhythm such as may occur occasionally in a general population without neurologic disease. Their tracings may be viewed as on the borderline of normal. Similarly, Case 5 may simply represent maturational changes in a normal child. Thus, to us, only Cases 8 and 15 seem to be unquestionably abnormal, and in Case 15 the antecedent head trauma may possibly have played a role in the genesis of the theta rhythms.

The findings of our study support the conclusion of Stewart[2] that generalized intracranial pressure per se is not productive of an abnormal electroencephalogram. In contrast, our previous study had suggested that increased pressure within the third ventricle, comparable to Stewart's increased intraventricular pressure, generated diffuse electroencephalographic abnormality. So-called monorhythmic delta activity is common in obstructive hydrocephalus, and, recently, Cordeau[9] has offered evidence that excitation of the medial-dorsal area of the thalamus gives rise to this rhythm, thus further strengthening our view. We have concluded that, in dealing with increased intracranial pressure, the electroencephalographer must consider not only the age of the patient and the acuteness of the rise of intracranial pressure but also the mechanisms by which intracranial hypertension develops.

Finally, we would comment briefly on the significance of obesity, which seems more than a chance occurrence in these patients. In view of Stewart's[2] observations on the generation of intracranial hypertension by extracranial occlusion of the veins draining the intracranial cavity, we wonder about the possibility of mechanical obstruction to venous drainage as a result of marked obesity. The high incidence of obesity, as well as fluid retention syndromes in general, among women may account for the sex difference.

SUMMARY

Electroencephalographic recordings were made in 16 patients with benign intracranial hypertension (pseudotumor cerebri). In the majority of patients, the recordings were within normal limits. The recordings of only 2 patients showed unequivocal abnormality, which consisted of bursts of theta rhythm.

The frequency of normal recordings in these patients contrasts strikingly with the high incidence of abnormal recordings in patients with obstructive hydrocephalus. These findings are consistent with the hypothesis that benign intracranial hypertension results from generalized intracranial rather than intraventricular hypertension.

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Orthostatic hypotension as the presenting sign in craniopharyngioma

Case report

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STUDENTS OF ORTHOSTATIC HYPOTENSION are well aware of the fact that disease of the central nervous system may manifest itself in disturbance of blood pressure. Because of the prominent role of the autonomic nervous system in the production of postural hypotension, it has been postulated that lesions of the hypothalamus, which is an important site of higher autonomic centers, could produce this syndrome. Extensive experimental evidence can be collected to show that regulation of vasomotor activity is among the functions of the hypothalamus,[1–6] although vasomotor centers in the brain stem also have been found to be important.[7–10] Recently, we had the opportunity to observe the clinical counterpart of this situation in a patient with a craniopharyngioma manifested initially by orthostatic hypotension. A report of this case is desirable because of its rarity and its interesting diagnostic aspects.

REPORT OF CASE

A 52-year-old white farmer came to the Mayo Clinic in November 1959 because of several months' history of exertional dyspnea, wheezing, unproductive cough, and fatigue. Bifrontal headache had been present for several years but had not been a real problem. Libido had been absent for some time. He had been given intermittent, short-term treatment with prednisone and ACTH at home without benefit.

Mild asthmatic bronchitis was evident on general physical examination. Pigmentation of the skin and external secondary sex characteristics were not abnormal; the testes were small, and the prostate gland was small and flat. The chief finding was that of orthostatic hypotension. The blood pressure was 110 mm. Hg systolic and 68 mm. diastolic in recumbent position, with a pulse rate of 80 per minute. When the patient sat up, blood pressure fell to 80/60 mm. and, when he stood, to 70/50 mm. When the patient stood up, the pulse became weak and rapid and he felt faint. On tilt-table testing, there was a progressive fall of the blood pressure as the patient was successively raised from a horizontal to a head-up position of 50 degrees (see table).

Laboratory tests did not reveal abnormalities of serum electrolytes, red and white blood counts, blood sugar, sedimentation rate, or urine. The specific gravity of the urine was 1.018.

Results of the neurologic examination were normal, as were roentgenograms of the skull. An electroencephalogram revealed generalized dysrhythmia, grade 2, which, although abnormal, was of no localizing value. The abnormality was not the same as that occasionally associated with lesions involving the midline structures of the brain.

Urinary excretion of 17-ketosteroids totaled 2.5 mg. per twenty-four hours; urinary excretion of corticosteroids measured 1 mg. per twenty-four hours by the formaldehydrogenic

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TILT-TABLE TEST

Position	*Time*	*Blood Pressure (mm. Hg)*	*Pulse*
Lying flat on table		100/70	88
		104/78	88
		100/70	80
		104/70	80
		100/80	88
Table tilted 10°	30 seconds	100/70	90
	45 seconds	100/80	96
	1 minute	90/70	96
Table tilted 20°	30 seconds	84/70	90
	40 seconds	96/70	90
	1 minute	100/74	96
Table tilted 30°	15 seconds	80/66	108
	45 seconds	90/70	96
	1 minute	90/70	
Table tilted 40°	30 seconds	76/?	102
	50 seconds	80/70	120
	1 minute	86/66	
Table tilted 50°*	40 seconds	60/?	96
	1 minute	60/?	96
	1 minute, 10 seconds	unobtainable	
Lying flat	15 seconds	80/62	
	30 seconds	86/66	
	45 seconds	90/70	
	1 minute	94/70	96
	1 minute, 55 seconds	104/80	102

*Note the fall in blood pressure to low and finally unobtainable levels.

method. Repeated determinations of plasma cortisols on successive days showed levels at 8 A.M. of 7.4, 7.9, and 6.9 μg. per 100 cc. of plasma, with levels at 3:30 P.M. of 9, 5.9, and 5.2 μg. After three days of stimulation with ACTH gel, 40 units twice daily, the excretion of 17-ketosteroids rose to 18.5 mg. and that of corticosteroids to 8.34 mg. for twenty-four hours. Plasma cortisols at 8 A.M. measured 45 μg. per 100 cc. and at 3:30 P.M., 44 μg. The value for urinary pituitary gonadotropin determined by the method of Albert was zero. The Soffer water test was carried out with ingestion of 1,500 cc. of water, after which the patient excreted only 500 cc. of urine in five hours. Although the values were comparable to those obtained for patients with pituitary or adrenal insufficiency, the presence of the orthostatic hypotension made the interpretation of the result dubious.

Sweating was tested over the entire body and face and was normal everywhere except over the hands (Fig. 1).

The cause for the postural hypotension remained uncertain, and therapy with 9-alpha-fluorohydrocortisone in doses of 1 mg. twice daily was started on an empiric basis. The symptomatic response was good, and the patient was dismissed.

Two weeks later, he returned complaining

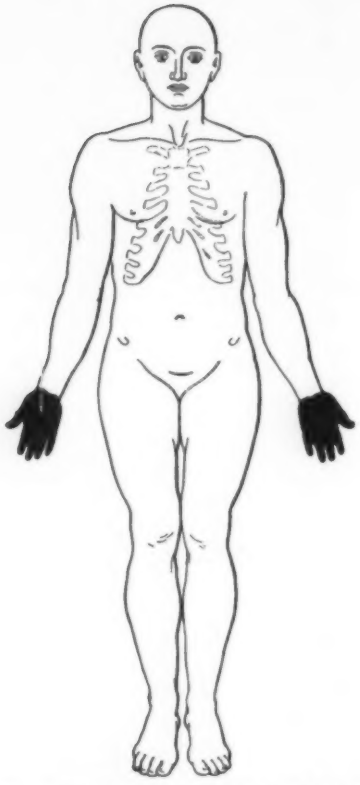

Fig. 1. Sweating was absent in the blackened areas.

bitterly of frontal headache. It now was aggravated by any change in position of the head and occasionally awakened him at night.

The results of general physical examination again were negative. Body temperature was 101° F. orally. His blood pressure was 112/72 mm. supine and 90/60 sitting. The values for serum electrolytes, carbon dioxide, blood urea, and sedimentation rate were normal. Protein-bound iodine measured 5.5 μg. per 100 cc. of serum. Plasma cortisols on the day after his admission measured 0.5 and 0 μg. per 100 cc., with an increase the next day to 4.4 μg. at 8 A.M. and 2.9 at 3 P.M. The initial values were thought to indicate suppression of normal ACTH stimulation of the adrenals due to the 9-alpha-fluorohydrocortisone. However, the low levels the next day suggested that normal stimulation of the adrenals by endogenous ACTH may have been lacking. When the administration of hydrocortisone was started four days after admission, the fever was reduced promptly and the clinical status was generally improved. Five days later, after regular administration of hydrocortisone in divided doses, frank diabetes insipidus developed with an 1,800- to 9,000-cc. output of urine with random specific gravities of 1.002 to 1.006. Hydrocortisone was continued because it was felt that there was definite impairment of anterior as well as posterior pituitary function.

Episodes of confusion were noted again, and lumbar puncture revealed an initial pressure of 80 mm. H_2O. Unfortunately, the patient was restless and the puncture was traumatic, showing bloody spinal fluid with 200,000 erythrocytes, 117 lymphocytes, 53 polymorphonuclear cells, and a protein content of 750 mg. per 100 cc. (corrected for blood of 486 mg. per 100 cc.). Sugar and chloride in the spinal fluid were normal. The spinal fluid was reexamined four days later; this time, the protein content was 160 mg. with 5 lymphocytes, 1 polymorphonuclear cell, and 5,546 erythrocytes. A smear of the spinal fluid, cultures for Mycobacterium tuberculosis and for fungi, and guinea pig inoculations were negative. Neurologic examination this time revealed a suggestion of bilateral lower quadrantic defect of the visual fields but was otherwise normal. Reading vision was 14/21 in both eyes. The visual fields were plotted and gave the following results: In the right eye, there was definitely an inferior temporal defect, splitting the midline; in the left eye, although the defect was mostly in the inferior temporal field, there was also slight encroachment on the inferior nasal field (Fig. 2).

In view of the history of the increasing stress-type headache, the postural hypotension, the recent development of diabetes insipidus, the evidence for anterior pituitary failure involving production of pituitary gonadotropins and ACTH, and the bilateral visual field defects, it was now evident that we were dealing with a space-consuming lesion in the region of the hypothalamus and impinging on the

optic chiasm. The presence of craniopharyngioma seemed a good possibility. On December 30, 1959, a right carotid angiogram showed evidence of some asymmetry in the upper portions of the siphon and its bifurcation; however, no definite suprasellar mass could be detected.

After preparation with depot cortisone and without further diagnostic procedures, right transfrontal craniotomy was performed; when the dura was opened along the right sphenoid ridge, both optic nerves and the anterior portion of the chiasm were visualized and all appeared normal. The pituitary gland was situated deep in the sella turcica and obviously was not causing pressure on the visual apparatus. A small spinal-puncture needle was introduced into what was thought to be the pituitary gland to exclude the possibility of a cyst or an aneurysm; only a few granules of tissue were obtained. Further dissection was done backward over the chiasm; both anterior cerebral arteries were displaced backward and upward, and it was now obvious that the chiasm was broader and yellower than the rest of the visual apparatus. The usual evidence of a normal anterior inferior third ventricle was absent. A spinal-puncture needle was introduced behind the chiasm between the optic tracts where a bulge appeared, and 5 cc. of thick yellow fluid was aspirated. Several pieces of solid tissue were removed for microscopic examination and proved to be part of a cystic craniopharyngioma. At no time was spinal fluid obtained, which suggested that the inferior portion of the third ventricle was occupied by a tumor. No further removal of the mass was attempted.

The patient made a satisfactory postoperative recovery, but, despite the daily administration of Pitressin, the fluid exchange remained high. Cortisone (10 mg. every eight hours) and posterior pituitary powder intranasally as necessary were given, and he seemed much improved generally.

X-ray therapy to the sellar region was begun. After 16 treatments, it had to be discontinued because of the patient's increasing confusion and drowsiness. Ophthalmologic examination early in March 1960 revealed the same findings as had existed preoperatively. He improved and was dismissed several weeks later.

On March 25, he was readmitted because of increasing confusion, shortness of breath, and dizziness on changing position. His blood pressure was 105 mm. Hg systolic and 70 mm. diastolic in the recumbent position and 90/65 mm. in the standing position, with a pulse of 84 per minute. He also complained of more headache than before. A pneumoencephalogram was made which showed evidence of a large rounded mass occupying the anterior and middle thirds of the third ventricle. On the same day, after preparation with supportive adrenal steroids, reelevation of the right transfrontal craniotomy flap was carried out and transventricular removal of a huge cystic craniopharyngioma was accomplished. The postoperative course was stormy, the blood pressure falling repeatedly to critically low values. Despite large doses of adrenal corticosteroids, the patient's condition remained unchanged and hypotension remained a grave problem.

Over subsequent weeks, gradual improvement occurred. Although the blood pressure has remained low, averaging 90 mm. Hg sys-

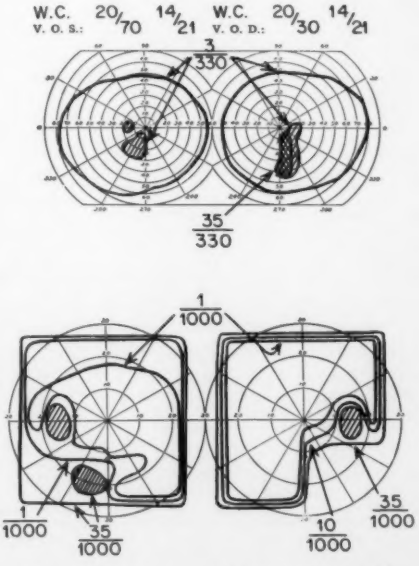

Fig. 2. Inferior temporal scotomatous field defect in each eye. The defect in the left eye has an arcuate character.

tolic and 60 mm. diastolic, it is not a critical problem. At the time of last report, the patient was still hospitalized. His neurologic condition had remained stable without gross neurologic deficit other than the visual field defect. He continued to be confused and still had evidence of moderate diabetes insipidus.

COMMENT

The association of intracranial tumors with orthostatic hypotension must be a rare occurrence. We have encountered only 3 such cases in the literature. In 1931, Schellong[11] published his observations of this syndrome in patients with hypopituitarism. In an addendum to his paper, he cited a case of pituitary tumor with orthostatic hypotension. Terzian,[12] in 1955, described 2 cases of parasellar tumors in which the presenting symptom was postural hypotension. Neither case was confirmed by operation or necropsy.

Wagner,[13] in his review of orthostatic hypotension, made the following statement: "Persistent orthostatic hypotension was found in an elderly woman with multiple cranial nerve lesions caused by a large brain tumor in the floor of the 4th ventricle."

Hypotension without postural component in cases of craniopharyngioma, chiasmal gliomas, and pituitary adenomas is a well-known observation and was referred to by Cushing[14] in 1930. Also, Ask-Upmark[15] has reported this finding with tumors of the basal structures of the brain in and around the sella turcica.

The pathogenesis of orthostatic hypotension has remained conjectural to the time of this writing. Most authors agree that, in the majority of cases, dysfunction of the sympathetic nervous system causes inability of the organism to respond by reflex vasoconstriction to changes from the recumbent to the erect position. On the basis of clinical observations, there is little doubt that the site of the lesion disrupting this reflex arc can occur at any level. This fact is attested to [1] by involvement of the hypothalamus in the cases of Terzian as well as in our patient, [2] by a patient with multiple infarcts in both cerebral hemispheres,[16] [3] by the occurrence of orthostatic hypotension in cases of Wernicke's encephalopathy,[17] [4] by a case of severe acute inflammation of the medulla diagnosed at necropsy,[18] [5] by a patient with Guillain-Barré syndrome,[19] and [6] by the association of this syndrome with tabes dorsalis,[13,20,21] hematomyelia and syringomyelia,[20] and traumatic transection of the spinal cord and after chordotomy.[22] Involvement of the peripheral nervous system with accompanying orthostatic hypotension has been encountered in cases of visceral neuropathies due to diabetes mellitus and in amyloidosis.[13] Also, thoracolumbar sympathectomies have been followed by postural hypotension.[23,24]

Recently, Shy and Drager[25] reported 2 cases of orthostatic hypotension with signs and symptoms referable to the central nervous system. Necropsy, performed in the most advanced case, showed pathologic changes in the autonomic ganglia, spinal cord, medulla, cerebellum, pons, midbrain, hypothalamus, and basal ganglia. The authors concluded that a primary degenerative disorder of the nervous system might be an etiologic factor in idiopathic orthostatic hypotension. The symptomatology in their cases suggested it to be a recognizable clinical syndrome. A comparable case was cited by Wagner.[13]

In our patient, the initial presenting symptom of the intracranial mass was orthostatic hypotension. This disturbance of regulation of blood pressure probably dated back at least to the early part of 1958, when he had consulted physicians at the Mayo Clinic regarding nephrolithiasis. On physical examination then, the patient complained of mild lightheadedness when sitting up quickly. His blood pressure was 90 mm. Hg systolic and 70 mm. diastolic. This problem was not investigated further at that time. When we saw the patient in December 1959, postural hypotension was an important clinical manifestation and the question of idiopathic orthostatic hypotension was raised. Several features, however, militated against it. Lack of anhydrosis made the diagnosis untenable in the sense suggested by Bradbury and Eggleston.[26] While our patient did exhibit acceleration of the pulse on assuming the erect position, this symptom did not exclude the diagnosis of idiopathic orthostatic hypotension. Furthermore, we were puzzled at the time by the fact that the patient did not exhibit the characteristic drop in blood pressure after exercise, a condition which has

been observed recently by members of our group in several other patients with idiopathic orthostatic hypotension.[27]

Orthostatic hypotension of Addison's disease or of adrenal insufficiency secondary to anterior pituitary failure would certainly be expected to be corrected completely by 2 mg. of 9-alpha-fluorohydrocortisone daily. However, the low base-line values of plasma cortisols and 17-ketosteroids suggested that there was indeed secondary adrenal insufficiency. The clinical response to hydrocortisone was further evidence of adrenal insufficiency. The lack of libido and the absence of pituitary gonadotropin on 2 occasions were evidence in support of pituitary gonadotropic failure. Results of the Soffer water test may have indicated anterior pituitary failure, or they may have been caused directly by orthostatic hypotension.

As the disease process advanced and headache with marked stress component became apparent, the possibility of an intracranial lesion was considered. With the development of diabetes insipidus which, possibly by coincidence, followed the administration of a powerful salt-retaining hormone far in excess of physiologic doses, additional support was lent to such a diagnosis. Final confirmatory evidence was bitemporal quadrantic hemianopsia.

CONCLUSIONS

In any patient with orthostatic hypotension, the search for a space-consuming intracranial lesion should be part of a thorough diagnostic investigation. Tumors of the parasellar and intrasellar regions may manifest themselves by disturbance of orthostatic blood pressure regulation. In our patient with a craniopharyngioma, the initial picture was that of orthostatic hypotension. Hypotension had been present to a mild degree for about two years, accompanied by an occasional headache, before it became incapacitating and before other symptoms and signs appeared betraying the true nature of the underlying lesion. Surgical removal of the tumor did not alter the orthostatic hypotension appreciably.

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Studies on the metabolism of diphenylhydantoin (Dilantin)

Eugene W. Loeser, Jr., M.D.

SINCE THE INTRODUCTION of phenobarbital[1,2] and diphenylhydantoin (Dilantin),[3,4] their use in the treatment of convulsive disorders has been empirical. While these drugs are effective in a large proportion of patients, individual variation in response to treatment has been unexplained. The possibility of variation in metabolism of anticonvulsant drug as an explanation of variation in response led to the present investigation.

In 1940, a method of measuring diphenylhydantoin levels was introduced.[5–9] Blood levels were recorded in the range of 30 to 60 μg./cc. for a diphenylhydantoin dose of 300 mg. per day. This procedure was considered too insensitive by later workers.[10] A spectrophotometric method[11] was reported that was more rapid and, in addition, could separate diphenylhydantoin and phenobarbital with reasonable accuracy. The blood level by this method ranged from 2 to 14 μg./cc. for a mean dose of 4.2 mg. per kilogram in 2 patients.

A third method utilizing a colorimetric technic was recorded by Dill and associates.[10] Blood samples from 4 patients on chronic administration of 1.2 to 4.2 mg. of diphenylhydantoin per kilogram varied from 0.9 to 10.5 μg./cc., although the level was fairly uniform for a given patient over the course of a day. After a single dose of 400 mg. of diphenylhydantoin sodium to each of 6 subjects, the highest level reached was 4.9 μg./cc. (in twelve hours). The decline in blood level was calculated to be 50% in eighteen to twenty-four hours.

More detailed studies, utilizing an adaptation of the methods of Dill and associates[10] and Plaa and Hine,[11] have been reported.[12] The blood levels increased, in general, with increasing doses of diphenylhydantoin. Blood levels of 10 to 20 μg./cc. were attained within ten to twelve days.

Information on the metabolism of diphenylhydantoin was contributed by Butler,[13] who found a pharmacologically inactive hydroxylated urinary metabolite to account for about half of the ingested dose of diphenylhydantoin.

Extensive free and radioactive diphenylhydantoin determinations[16] suggested that diphenylhydantoin and/or its metabolites are excreted into the gastrointestinal tract via the biliary system and reabsorbed to be excreted in the urine.

SUBJECTS AND METHOD

The method of Dill and associates[10] for the determination of diphenylhydantoin has been used in the present study. Samples consisting of 10 cc. of blood were drawn from normal controls, patients hospitalized or attending the Out Patient Department at North Carolina Memorial Hospital, and institutionalized patients at Butner and Raleigh (N. C.) State hospitals. The blood was collected either dry for serum or in oxalated tubes for plasma. All determinations were run in duplicate with routine samples of 1 to 3 cc. Samples antici-

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pated to contain high concentrations were run with 0.5 cc., in compliance with the limitation of the procedure in quantitatively coloring over 40 μg. in the original sample.

The countercurrent extraction for separation of phenobarbital was not utilized, so that patients for whom diphenylhydantoin alone was prescribed were studied.

RESULTS

The addition of known quantities of diphenylhydantoin to pooled blood bank plasma resulted in an average recovery of 95% on duplicate determinations of 34 pools. For levels between 5 and 30 μg./cc., recovery ranged from 94 to 98%. The recovery fell to 90 to 93% for levels above 30 μg./cc.

Pooled plasma blanks ranged from 0.1 to 0.5 μg./cc., with an average of 0.3 μg./cc.; 23 patients and normal controls on no medication gave duplicate blanks of 0 to 1.3 μg./cc., with an average of 0.3 μg./cc. (± 0.34). Two-thirds of the control blanks were 0.3 μg./cc. or less. Pooled specimens from patients on prochlorperazine (Compazine), chlorpromazine (Thorazine), and trifluprom azine (Vesprin) gave values within the control range.

Oral administration of diphenylhydantoin. Diphenylhydantoin blood levels were determined in 7 nonepileptic institutionalized subjects on no medication. The undivided oral dose was administered daily at the same time for a thirteen-day period. The average dose was 4.4 mg. per kilogram (range, 2.7 to 7.9 mg. per kilogram). Daily blood samples for nineteen days, taken at an average of eighteen hours after the administration of diphenylhydantoin, showed variation in the rate of rise and the height of levels attained from patient to patient. The time for peak levels varied from one day to the thirteen days that therapy was continued. The peak levels varied from 2 to 47.7 μg./cc. (Fig. 1).

After discontinuation of diphenylhydantoin, control levels were reached as early as one to two days in subjects with low peak levels. In the subject with the highest attained level, a significant blood level was still present after six days.

A plot of the ratio of blood level to diphenylhydantoin dose in milligrams per kilogram shows a pattern of curves similar to Figure 1 and indicates that the variation from patient to patient is not strictly dose-dependent.

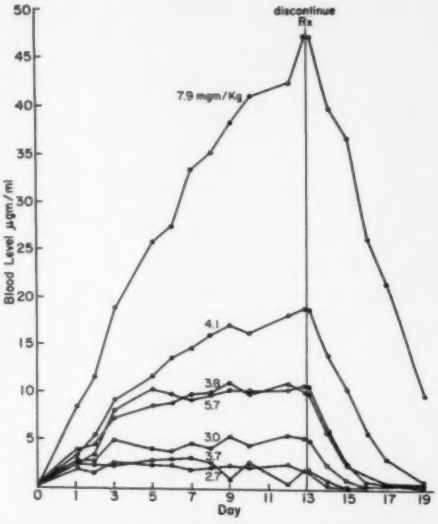

Fig. 1. Daily blood levels in 7 patients after starting on daily oral diphenylhydantoin in milligrams-per-kilogram dose noted. Drug was discontinued after thirteen days. Levels are recorded in micrograms per cubic centimeter.

Random blood determinations of diphenylhydantoin were made on 29 patients with seizures for whom diphenylhydantoin had been prescribed in a constant dose for over two weeks (Fig. 2). The average dose was 5.4 mg. per kilogram (range, 3.3 to 8.8 mg. per kilogram; 66 to 600 mg.). The average blood level was 9.5 μg./cc. (range 2.5 to 42.1 μg./cc.).

The average dose prescribed for 20 outpatients was 5.5 mg. per kilogram. Inpatients, considered separately because of the more controlled conditions under which medication could be administered, received an average dose of 5 mg. per kilogram. The blood level in the outpatient group averaged 9.2 μg./cc. (2.5 to 28.2 μg./cc.), whereas the inpatient group averaged 10.5 μg./cc. (5.2 to 23.3 μg./cc.).

While the average blood levels are higher

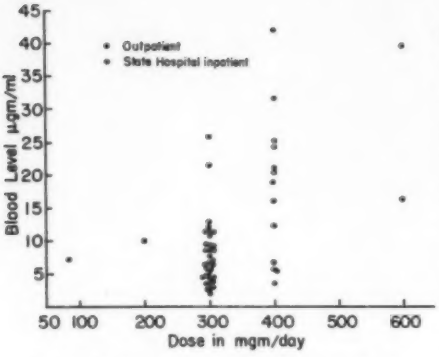

Fig. 2. Diphenylhydantoin blood levels. Each point represents average of duplicate determinations on each sample obtained after patient had been on a given dose for at least two weeks.

with increasing dose, statistical analysis indicates that the blood levels do not vary significantly with dose (Fig. 3). The differences in average blood level and dose between the inpatient and outpatient groups are also not statistically significantly different.

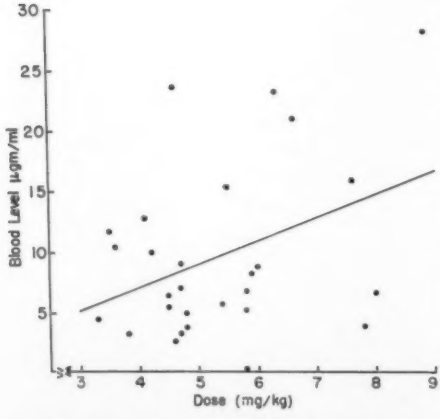

Fig. 3. Diphenylhydantoin blood levels. Each point represents average of all determinations after patient had been on a given dose (in milligrams per kilogram) for at least two weeks. Line represents expected average blood level for a given dose. Slope of line is not significantly different from zero.

Intravenous administration of diphenylhydantoin. To study the effect of absorption on the variable rate of rise and level attained after daily oral administration, single daily intravenous diphenylhydantoin injections were administered to 4 of the subjects studied in the daily oral dosage experiment. The dose of diphenylhydantoin given intravenously was the same as had been given orally to each subject. The daily administration of intravenous diphenylhydantoin for seven days produced rises in the blood levels which paralleled those for oral administration (Fig. 4).

The decline in blood levels was determined in 3 patients after the administration of an average single intravenous dose of 4.6 mg. per kilogram. Serial determinations indicated a 10% rate of decline in blood level per hour. One hour after injection, the blood level averaged 7.6 µg./cc. (range, 6 to 9.5 µg./cc.); twenty-four hours after injection, the levels averaged 2.5 µg./cc. (range, 1.5 to 3.8 µg./cc.). This compares with the value twenty-four hours after an average single oral dose of 4.5 mg. per kilogram (average, 3.7 µg./cc.; range, 2.2 to 8.5 µg./cc.).

Divided versus single daily diphenylhydantoin dosage. The rate of rise and peak level attained with divided doses of diphenylhydantoin was compared with single daily administration in 2 subjects. The same total dose, divided into 2 doses per day, was given as had been given in single dose. The parallel rises in blood levels are shown in Figure 5.

Toxicity. Only 2 patients with toxic symptoms were studied; 1 patient had been on a daily dose of 6.2 mg. per kilogram (400 mg.) for two months before the development of ataxia. The blood level in 2 separate samples at the peak of symptoms averaged 46.1 µg./cc. The second patient was seen twenty hours after attempted suicide by the ingestion of 62 diphenylhydantoin capsules (100 mg. per kilogram) and several hours after gastric lavage in an outside hospital. Cerebellar signs were marked. The patient was alert and oriented. The blood level was 37.7 µg./cc.

The only subject without toxic symptoms who had a blood level in this high range reached 47.7 µg./cc. on a dose of 7.9 mg. per kilogram (500 mg.) after thirteen days of daily administration.

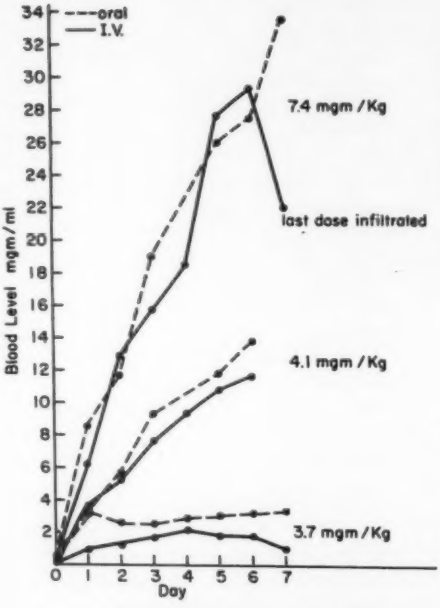

Fig. 4. Reproduction of 3 curves (broken lines) from Figure 1. Comparison of daily intravenous administration of diphenylhydantoin with daily oral administration for seven days. A fourth subject so studied had blood levels in same range as represented in lower curve and is not shown. Last intravenous dose in upper curve infiltrated, and actual effective dose is unknown.

Cerebrospinal fluid and saliva. The highest spinal fluid recorded was 3.1 μg./cc. The average for 4 determinations was 1.5 μg./cc., while blood levels simultaneously averaged 8.3 μg./cc. Saliva samples obtained from 2 patients without gum hypertrophy contained 1.1 and 0.1 μg./cc., with simultaneous blood levels of 9.8 and 3.7 μg./cc., respectively.

Protein binding. In vitro dialysis revealed the major binding of diphenylhydantoin to be to the albumin fraction of serum protein. The fraction bound was proportional to the albumin concentration with an average of 77% bound at a level comparable to normal serum. Similar data obtained with phenobarbital[17] is compared with diphenylhydantoin in Figure 6. Preliminary observations in 7 patients indicated no correlation between

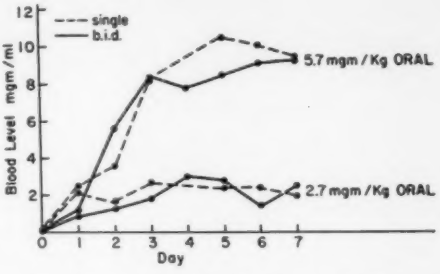

Fig. 5. Reproduction of 2 curves (broken lines) from Figure 1. Comparison of twice a day oral administration with single daily administration for seven days

diphenylhydantoin blood level and serum albumin concentration.

DISCUSSION

The average blood levels reported are in fair agreement with previous studies.[10,12-14] It should be stressed, however, that the range of values obtained both in epileptic and non-epileptic subjects was considerable.

The time for blood level to reach a plateau varied over a wider range than reported by Buchthal, Svensmark, and Schiller.[14] The present data indicate the time to vary from one to

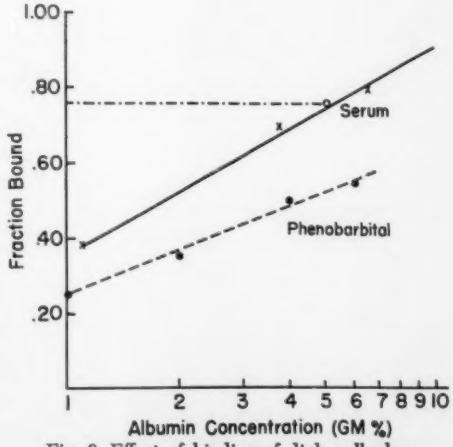

Fig. 6. Effect of binding of diphenylhydantoin with increasing concentration of albumin. Phenobarbital data, Reference 17

at least thirteen days, compared to the six to ten days reported by Buchthal and associates. The same authors state that the frequency of convulsions is reduced to one-half or less with a serum diphenylhydantoin level over 10 μg./cc. and that 86% of patients are improved with levels over 15 μg./cc. Of the blood levels shown in Figure 1, those of 3 of the 7 subjects failed to reach a level of 10 μg. after thirteen days (diphenylhydantoin dose, 2.7, 3, and 3.7 mg. per kilogram per day). Only 2 subjects reached 15 μg./cc. (diphenylhydantoin dose, 4.1 and 7.9 mg. per kilogram per day).

Chronic administration of diphenylhydantoin to patients on an outpatient basis results in random blood levels with a greater scatter and lower average than subjects treated in a hospital setting. The difference in average blood level in the inpatient and outpatient groups is not statistically different. Neither irregular diphenylhydantoin medication nor covert barbiturate ingestion can be ruled out as possible causes for the scatter seen in the outpatient blood levels.

The comparable rise in blood levels after administration of the same dose of diphenylhydantoin in oral and intravenous form rules out absorption as a factor in the variability of blood level in individual patients. The parallel rise with these two routes of administration obviates any advantage to elective parenteral therapy in long term treatment.

The similarity in the rate of rise and the peak levels attained with single and divided administration of diphenylhydantoin is in agreement with the findings of Buchthal and associates.[14] However, they reported a 30 to 50% variation between a day's high and low level with single daily diphenylhydantoin administration and have suggested that the drug be given every twelve hours.

Withdrawal of anticonvulsants may be accompanied by increasing frequency of convulsions.[19] It has been shown, however, that abrupt discontinuation of diphenylhydantoin is attended by a gradual fall in blood level over a period of one to six days. Similarly, after withdrawal of phenobarbital, blood level declines at a rate of about 15% a day.[20] Whether a fall to an absolute level or the rate of fall is significant in the induction of withdrawal seizures is unknown.

Since the data presented indicate adequate absorption of oral diphenylhydantoin, possible variations in handling of the metabolic product 5-(4-hydroxyphenyl) 5-phenyl hydantoin (HPPH) may have bearing on variation in blood level of the parent drug. This compound is pharmacologically inactive.[15,18] In 2 persons studied,[15] conjugated HPPH in the urine accounted for 44 and 62% of the daily dose of diphenylhydantoin.

The role of tissue level rather than blood level in seizure control and toxic effects has not been investigated. In rats, brain level closely parallels the rise in plasma level after a single oral dose of diphenylhydantoin.[10] This suggests that the study of serum may well reflect the pertinent tissue level. On the other hand, the levels in rat fat and liver were considerably higher than either brain or serum. The possibility of concentration and binding of drug in tissues unrelated to therapeutic or toxic action of diphenylhydantoin may also play a role in variable blood level.

SUMMARY

Diphenylhydantoin blood levels were determined by the technic of Dill and associates.[10]

The rise to peak blood level with daily oral diphenylhydantoin administration varied from one to at least thirteen days. The peak levels attained varied from 2 to over 40 μg./cc. after thirteen days of drug administration. The rates of rise and peak levels attained are, in general, directly related to dose, but the variation from patient to patient is not solely dose-dependent.

The time for decline in blood levels to control values varied from one to at least six days. The hourly decline in blood values after a single intravenous dose approximates 10%.

Blood samples from patients on a constant dose of diphenylhydantoin averaged 9.5 μg./cc. The values ranged from 2.5 to over 40 μg./cc. In general, the blood level varied directly with dose, but the correlation of blood level variance with dose is not statistically significant.

Intravenous diphenylhydantoin and oral medication divided into twice a day dosage

produced a rate of rise and peak level comparable to single daily oral administration.

Possible factors which could play a role in blood level variability from patient to patient are discussed.

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Corrigendum: On page 261 of the March issue of NEUROLOGY in the article "Observations on Ceruloplasmin and Methods for Its Estimation," the section headed TEST PROCEDURE should read: "Place 1 cc. of PPD solution in a 15-cc. test tube, add 0.1 cc. serum or other material, and allow to stand in a water bath at 37° C. for fifteen minutes;" etc.

Multiple diverse primary brain tumors

Report of a case with review of literature

M. J. Madonick, M.D., J. H. Shapiro, M.D.,

and R. M. Torack, M.D.

DIVERSE PRIMARY MULTIPLE BRAIN TUMORS are not common. Wilson[1] collected 11 instances. The table summarizes a survey of the literature for further examples of this condition. We have excluded the 3 cases of Feigin and Gross[32] of sarcomas arising in the hyperplastic blood vessels of a glioblastoma, the individual cases of French[33] and Bailey and Ley,[34] in which astrocytoma and perithelial sarcoma were apposite, and the case of Fine, Paterson, and Gaylor,[35] in which a vascular malformation, an angioma, was associated with an intraventricular oligodendroglioma. For acceptance of a case, the tumors had to be in different locations of the brain and of different histologic structure.

This report records another example of diverse primary multiple brain tumors. The patient had 2 meningiomas and 1 glioblastoma multiforme and, in addition, carcinoma of the breast. Angiographic appearance of 1 tumor was that of a meningioma; the only question was the type of the other tumor.

CASE REPORT

A 51-year-old deaf and dumb woman was seen on April 19, 1960. The history was obtained from her, from her deaf and dumb husband, and from their 14-year-old daughter, who spoke and who communicated with both her parents in sign language. The patient had had headaches for three weeks with recent blurring of vision; she was becoming sleepy. Her appetite had been poor, but there was no weight loss.

General physical examination was normal. The pulse rate was 90. Pulsations in both carotid arteries were normal.

On neurologic examination, she was drowsy. She veered to the right on walking. She had left central facial paresis, especially on smiling. There was no evidence of dysphasia. The deep reflexes were brisk. A left Babinski sign was demonstrated. Papilledema with hemorrhages in the right fundus was noted.

On admission to the Montefiore Hospital on April 20, she was perhaps slightly more drowsy. The pulse rate was 80, the temperature 99° F., and the blood pressure 200/100 mm. Hg. A mass was found in the right upper breast. It was not fixed to the chest wall, although it was fixed to the skin. It had been noted by the patient three months previously.

An electroencephalographic examination was done the same day. Moderate to high voltage irregular activity, averaging 9 per second, was seen. Consistent theta activity was seen in the range of 5 to 6 per second throughout the record, and occasional delta waves of 2 per second emanating from the right hemisphere were noted, predominately from the posterior temporal area. Occasional theta activity was also seen in the left hemisphere with frontal predominance. A lesion in the right posterior frontotemporal region was suspected.

No abnormalities of the skull were seen on plain roentgenograms. Biplane bilateral carotid arteriography yielded the results shown in Figures 1 through 6.

A right temporal craniotomy was performed on April 22. A necrotic tumor of the right temporal lobe was found. Several pieces of tissue were removed, the largest being 1.5 x 1 x 0.4

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CASES OF MULTIPLE PRIMARY BRAIN TUMORS
DRAWN FROM THE LITERATURE

Author	Types of tumors	Plus
Austin, Barrows, and Grant[2]	Sarcomatous meningioma	Astroblastoma
Davison[3]	Ganglioneuroma	Glioblastoma
Adam-Falkiewiczowa[4]	Papilloma	Glioblastoma multiforme
Zülch[5]	Meningioma (2 cases)	Monostrocellular sarcoma Pituitary adenoma
Shapland and Greenfield[6]	Meningioma (optic nerve)	Neurofibromas of cranial nerves and central glioma
King and Botton[7]	Meningioma	Spongioblastoma polare
Barla-Szabó[8]	Meningioma	Glioma
Russell and Rubinstein[9]	Meningioma (5 cases)	Glioblastoma multiforme
Gardner and Turner[10]	Bilateral acoustic neuromas (Case I)	Meningioma
Worster-Drought, Dickson, and McMeneney[11]	Meningioma (Case I)	Neurofibromas
Gardner and Turner[12]	Meningioma	Acoustic neuroma
Turner and Gardner[13]	Multiple meningiomas (Case I)	Bilateral acoustic neuromas
	Meningioma (Case II)	Cranial nerve neurofibromas
	Meningioma (Case V)	Astrocytoma
Gass and Van Wagenen[14]	Meningioma	Malignant oligodendroglioma
Feiring and Davidoff[15]	Meningioma	Glioblastoma multiforme
List, Williams, and Balyeat[16]	Chromophobe adenoma	Glioblastoma multiforme
Love and Blackburn[17]	Chromophobe adenoma	Meningioma
Wise, Malamud, and Boldrey[18]	Chromphobe adenoma (2 cases)	Oligodendroglioma
Arieti[19]	Meningioma (2 cases)	Astrocytoma
Alexander[20]	Meningioma	Spongioblastoma ependymale
Kirschbaum[21]	Meningioma	Subependymal glioblastoma multiforme
Myerson[22]	Meningiomas (2)	Gliomas (4)
Cushing and Eisenhardt[23]	Meningioma	Glioblastoma
Hoffmann[24]	Astrocytoma	Cerebellopontine angle meningioma
Brihaye, Danis, and Drochmans[25]	Meningioma (optic nerve)	Glioma
Kessel[26]	Meningioma	Acoustic neuroma
Fényes and Kepes[27]	Meningioma (2 cases)	Glioma
Glass and Abbott[28]	Meningioma	Bilateral acoustic neuroma
Cowie[29]	Malignant glioma	Acoustic neurofibroma
Bartoloni[30]	Glioblastoma	Meningioma
Tolentino and Giammusso[31]	Glioblastoma multiforme	Meningioma

cm. and the smallest 0.3 x 0.4 x 0.3 cm. The specimens consisted of pale yellow, rubbery tissue which in part, at least, was covered by blood clot or hemorrhage. The largest specimen was soft and necrotic. The total weight of the specimens was 3 gm.

Histologic examination revealed fragments of a malignant gliogenous neoplasm. Most of the cells appeared to be astrocytes, and pleomorphism of the cellular elements, necrosis, pseudopalisading, giant cells, and areas of fresh hemorrhage were noted. The diagnosis was glioblastoma multiforme.

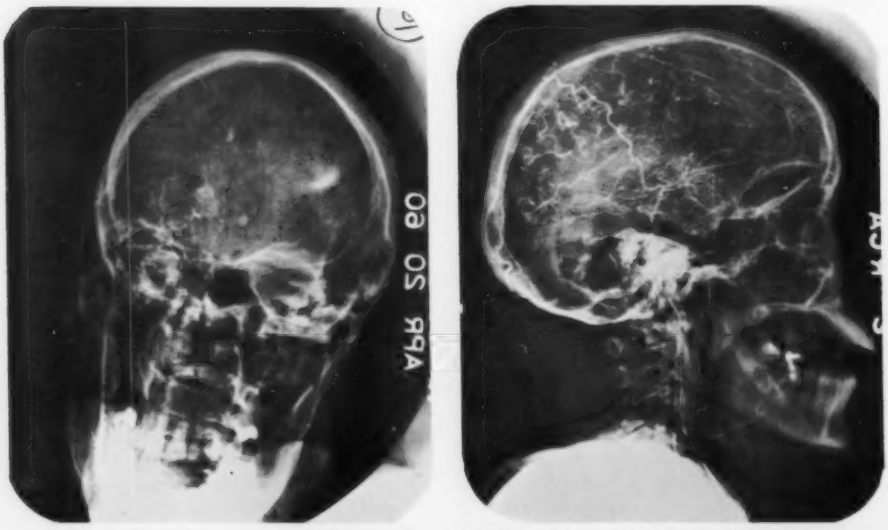
Six hours after operation, the patient was resting quietly and asking for water by sign language. Nine hours after operation, she was trying to explain things with her hands. Two hours later, she could not be roused; she died about thirty-six hours after operation.

Autopsy report. The unfixed brain weighed 1,284 gm. The attached portion of dura was covered by clotted blood. The right lateral

Fig.1. Right carotid arteriogram. Lateral projection. Arterial phase. Elevation of carotid siphon and middle cerebral artery. Uncoiling of anterior cerebral artery probably due to ventricular dilation

leaflet of the dura contained the craniotomy wound, which was closed by black silk sutures. The right cerebral hemisphere was larger than the left. Mild cingulate gyrus herniation from right to left and right uncal grooving measuring 0.8 cm. were seen. Most of the right temporal lobe was absent secondary to the surgical procedure. The brain surface in this area was not covered by leptomeninges and appeared hemorrhagic and ragged. A large concavity lined by intact leptomeninges was seen on the orbital surface of the left frontal lobe. The cavity was formed by a large extracerebral mass which was attached to the left sphenoid ridge and which measured 4 cm. in its greatest diameter. The cranial nerves, in particular the eighth, were unremarkable upon gross examination.

Coronal section of the cerebral hemisphere revealed a large infiltrating intracerebral neoplasm which measured 5.5 cm. in its greatest cross-section diameter (Fig. 7). It extended from the level of the genu of the corpus callosum to the level of the lateral geniculate body. It also involved the right putamen, the lateral margin of the right globus pallidus, and part



Figs. 2 and 3. Right carotid arteriogram. Frontal (left) and lateral (right) projections. Intermediate phase. 5-cm. zone of hypervascularity is present in middle fossa. Vascularity consists of many small vessels of irregular caliber.

Fig. 4 (right). Left carotid arteriogram. Frontal projection. Arterial phase. Distal carotid siphon is elevated and narrowed. Siphon is displaced medially. Only first portion of anterior cerebral artery is visualized, and this is narrowed. Proximal portions of anterior and middle cerebral arteries are elevated but not as much as on right.

of the right internal capsule. The mass was soft and partially necrotic and contained numerous foci of small hemorrhages. It was not well demarcated from the adjacent cerebral tissue.

On cut section, the tumor of the left sphenoid ridge was firm and granular. It was tan-gray with no foci of degeneration. The cortex underlying the mass appeared partially atrophic and partially absent (Fig. 7).

When the microscopic preparation of the intracranial mass was examined, a neoplasm composed largely of irregular astrocytes was observed. Numerous foci and necrosis were seen. Around many such areas of necrosis, spongioblasts were arranged in pseudopalisades (Fig. 8). Many multinucleated and pleo-

Figs. 5 and 6. Left carotid arteriogram. Frontal (left) and lateral (right) projections. Intermediate phase. Hypervascularity of cloud form over lesser sphenoid wing and extending medially to midline. Persistent arterial filling due to some extravasation at site of needle puncture

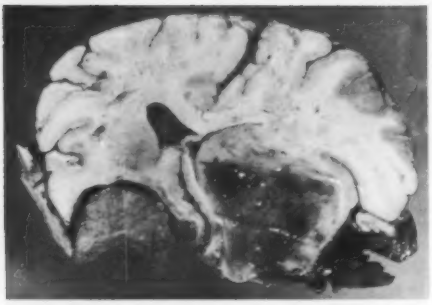


Fig. 7. Coronal section of cerebral hemispheres showing large infiltrating glioma in right cerebrum and left sphenoid ridge meningioma distorting posterior orbital surface of left frontal lobe

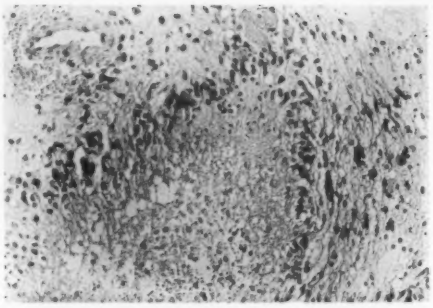


Fig. 8. Photomicrograph of right intracerebral neoplasm which demonstrates prominent necrosis surrounded by spongioblasts and bizarre astrocytes. Hematoxylin and eosin. × 450

morphic astrocytes were present. Vascular endothelial proliferation was a prominent morphologic feature. Occasionally, perivascular lymphocytic cuffs were noted. These structural characteristics identified the neoplasm as a glioblastoma multiforme.

The left-sided sphenoid ridge tumor, with hematoxylin and eosin preparation, was composed of numerous, elongated, regular cells. Mitoses were not seen. Many cells were arranged in interlacing bundles. Numerous cellular whorls were present throughout the specimen (Fig. 9). Occasional psammoma bodies were visible. There was no evidence of malignancy. This neoplasm was a classic meningocytic meningioma. A nodule, 1 cm. in diameter, not visualized on angiography was present on the inferior aspect of the right lateral dural leaflet; microscopic examination showed it to be a meningioma.

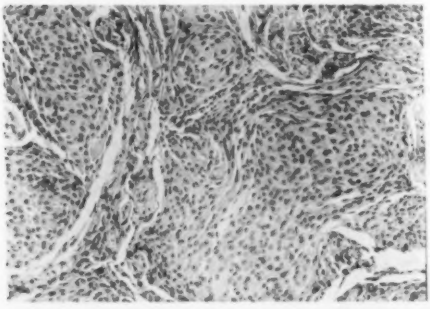


Fig. 9. A photograph of the sphenoid ridge meningioma which illustrates the prominent whorl formation. Hematoxylin and eosin. × 450

In Spielmeyer and Sudan IV preparations of the left oculomotor nerve, myelin destruction and free fat in this structure were seen. Similar stains of the facial and acoustic nerves were unrevealing.

Hematoxylin and eosin preparation of the right breast disclosed a malignant neoplasm composed of moderately large polygonal epithelial cells. They were arranged in small nests surrounded by abundant dense fibrous connective tissue. The cells had no characteristic architectural pattern. No evidence of metastases was present.

DISCUSSION

With few exceptions, in most of the previously reported cases, 2 diverse primary brain tumors were discovered at autopsy. In several instances, 1 tumor was found by radiologic studies or operation and the second tumor was demonstrated at autopsy. Thus, in Alexander's case,[20] 1 tumor was demonstrated by ventriculography. In the case of Gass and Van Wagenen,[14] 1 tumor was identified by its calcification on roentgenograms. List's[16] case included enlargement and destruction of the sella turcica and a shift of the pineal gland to the left. Feiring and Davidoff's[15] patient had

displacement of the right anterior horn; a right frontal meningioma was removed. Pneumoencephalography was then repeated; a shift from the left to the right side was then demonstrated, and a left frontal glioblastoma was found. A glioblastoma was found at operation in Cowie's[29] case. However, there was considerable erosion of the internal auditory meatus; at autopsy, an acoustic neurofibroma was confirmed. In Austin's[2] case, an astrocytoma was found after ventriculography and angiography (done on one side); at autopsy, a meningioma was demonstrated on the opposite side of the brain. In the case of Tolentino and Giammusso,[31] a large mass with a network of vascularity in the midline and involvement of both parietal areas and one temporal area were seen on bilateral carotid angiography; in addition, a small meningioma of the falx was also found. In the present case, the right carotid angiogram indicated a mass lesion in the right temporal area. Since a hard tumor was palpable in the breast, the possibility of the temporal lobe tumor being metastatic had to be considered. To exclude multiple lesions which would then preclude operation, an angiogram was done on the left side. Since this test demonstrated the classic appearance of a meningioma on the opposite side, a craniotomy was done on the right side and a glioblastoma was then found in the right temporal lobe. It is interesting to note that the most frequent combination of tumors, as seen in the table, is meningioma and glioblastoma. This is to be expected since the former is the most frequent of the nonmalignant and the latter the most frequent of the malignant brain tumors. Although the presence of multiple brain tumors may be detected on plain roentgenograms of the skull or by encephalography, the use of cerebral angiography may permit one to diagnose tumors of different histologic types as determined by the vascular angiographic patterns.

SUMMARY

A case of multiple primary brain tumors—glioblastoma with one large and a second small, nonsymptomatic meningioma—with carcinoma of the breast is described.

A summary of primary multiple brain tumors of different histologic structure, collected from the literature, is listed in the table.

The combination of glioblastoma multiforme and meningioma is the most frequent.

Angiography was of great aid in detecting the presence of two tumors. The presence of distinctive vascular angiographic patterns may be useful in the diagnosis of multiple diverse brain tumors.

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On the origin of the lipoproteins in the cerebrospinal fluid

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THE PROTEIN-BOUND LIPIDS in serum occur mainly in two fractions migrating with the α_1- and β-globulins, respectively. A paper electrophoretic analysis of cerebrospinal fluid for the occurrence of these two fractions in a clinical series was described in a previous paper,[1] in which the literature was also discussed. The α_1-lipoprotein fraction was demonstrated in most of the cases, and its occurrence or size did not appear to be related to neurologic disorders. On the other hand, the β-lipoprotein fraction was only found in samples from patients with known, severe neurologic disease and sometimes was the only abnormality demonstrable by laboratory methods. This prompted the present investigation of the lipoproteins in the cerebrospinal fluid.

In the discussion of the origin of the lipoproteins in the cerebrospinal fluid, three possible sources may be considered—the white cells, nervous tissue, and blood. On dissolution of the white cells, lipoproteins might be released into the cerebrospinal fluid, capsules of white cells being especially rich in these substances. This theory has been discussed by Bauer,[2] for example. But, since both the α_1-fraction and the β-fraction could be demonstrated in cell-free cerebrospinal fluid from patients without signs of meningitis,[1] the cells may probably be ruled out as an origin of the lipoproteins.

The other two sources appear more possible. Nervous tissue is extremely rich in lipids and, according to Smith and associates,[3] substances formed on catabolism of the lipids in the central nervous tissue could reasonably occur in the cerebrospinal fluid in health and disease. However, the occurrence of β-lipoprotein in the spinal fluid might also be a manifestation of some derangement of the passage of the proteins from the blood to the fluid owing to a neurologic disorder. Most of the cerebrospinal fluid proteins not containing lipid are probably derived from blood, and this might also hold for the lipoproteins.

By separating the cerebrospinal fluid proteins by immunoelectrophoresis, allowing the lipoprotein fractions thus separated to migrate toward the antibodies in antihuman serum, it should be possible by means of specific antigen-antibody reaction to ascertain whether the cerebrospinal fluid lipoproteins have the same properties as those from blood.

METHOD

Immediately after collection, the cerebrospinal fluid sample was centrifugated for twenty minutes, and the cell-free supernatant was carefully removed. The sample was then concentrated according to Mies.[4] Microimmunoelectrophoresis was performed by Heremans'[5] modification of the Scheidegger[6] method. Purified agar (Reinagar) and antihuman serum from Behringwerke, Marburg/Lahn, Germany, were used. The preparations were colored with Sudan black in alkaline ethanol according to a modification of the Swahn[7] method described by Uriel and Grabar.[8] No blood-stained samples were accepted. Serum, prepared from blood samples collected in the morning from patients in the postabsorptive state, was examined at the same time as the cerebrospinal fluid from the respective patients.

A slight modification of the method described by Waddell[9] was used for quantita-

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tive determination of the protein content of the cerebrospinal fluid sample before and after concentration. The amounts of the various protein fractions in the cerebrospinal fluid were determined by paper electrophoresis according to Laurell, Laurell, and Skoog.[10]

MATERIAL

The material consisted of cerebrospinal fluid samples from 15 patients with no symptoms or signs of neurologic disorder and from 44 patients with the following conditions:

	Cases
Epilepsy	9
Cerebral or spinal tumor	15
Multiple sclerosis	12
Meningitis	2
Healed spinal syphilis	1
Sequelae from encephalitis	1
Polyneuropathy	1
Collagenosis (?) with cerebral involvement	1
Spastic paraplegia	1
Paresis of sixth nerve	1

Most of the samples had been collected by lumbar puncture and the remainder by cisternal puncture. No distinction was made between the lumbar and cisternal samples.

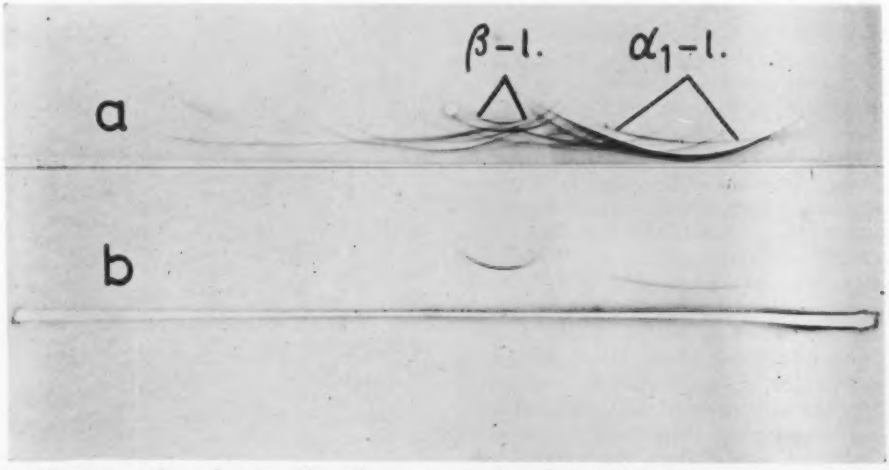
RESULTS

In all of the cerebrospinal fluid samples from patients with and without neurologic signs, the α_1 field contained a line stainable with Sudan black. In 14 cases, a line also occurred in the β-globulin field. The serum and cerebrospinal fluid were similar with respect to the appearance and site of these lines.

The upper half of the figure (a) shows an immunoelectrophoretic slide of a cerebrospinal fluid sample containing both α_1- and β_1-lipoprotein fractions. In this case, the proteins were stained with amido black, but the lipoproteins are then not perfectly distinguishable from the other protein fractions. When colored with Sudan black, the lipoproteins appear distinctly (see figure b).

In only one case was sudanophilic material found outside the α_1- and β_1-lipoprotein fractions and then in the γ-globulin fraction. The γ-globulin fraction in the corresponding serum did not show any such lipoprotein band. The cerebrospinal fluid sample had been tapped from a 48-year-old man with multiple sclerosis. At the time of the examination, he was severely disabled but had shown no signs of any recent new symptoms indicating an active phase of the disease.

The total protein concentration in the original and the concentrated cerebrospinal fluid and the amount of β-globulins in the 14 patients with a β-lipoprotein fraction are summarized in the table. It is clear from the table



Microimmunoelectrophoresis with antihuman serum of cerebrospinal fluid from a patient with cerebral tumor (Case 11) colored with [a] amido black 10 B and [b] Sudan black.

TOTAL PROTEIN CONTENT IN ORIGINAL CEREBROSPINAL FLUID AND CEREBROSPINAL FLUID CONCENTRATE AND PROTEIN CONTENT IN BETA-GLOBULIN BANDS IN 14 PATIENTS WITH BETA-LIPOPROTEIN FRACTION, OBTAINED BY MICROIMMUNOELECTROPHORESIS

Case number	*Diagnosis*	*Total Protein Content in mg. per 100 cc. Original cerebrospinal fluid*	*Concentrated cerebrospinal fluid*	*Content of beta-globulins in mg. per 100 cc.*
1	Epilepsy	30	572	4.5
2	Multiple sclerosis	42	2,008	5.8
3	Spinal tumor	42	2,020	5.7
4	Spinal tumor	57	1,052	8.1
5	Cerebral tumor	69	248	8.3
6	Cerebral tumor	72	3,020	9.4
7	Cerebral tumor	73	1,400	10.9
8	Porphyria with polyneuropathy	76	1,800	9.5
9	Cerebral tumor	83	2,980	11.5
10	Bacterial meningitis	140	3,680	–
11	Cerebral tumor	143	3,120	15.2
12	Herpes zoster with meningitis	218	5,200	21.8
13	Collagenosis (?) with cerebral involvement	340	4,100	45.6
14	Spinal tumor	620	4,280	65.7

that β-lipoprotein can occur in relatively low concentrations of the total proteins in the cerebrospinal fluid—lowest value, 30 mg. per 100 cc.—as well as in a low concentration of β-globulins. In addition, the β-lipoprotein fraction was demonstrated when the protein content of the concentrated cerebrospinal fluid was as low as 0.25 gm. per 100 cc. (Case 5). This indicates the high sensitivity of the microimmunoelectrophoretic method.

COMMENTS

The investigation showed that the proteins bound to the lipids in the α_1- and β-band in the cerebrospinal fluid are precipitated by the specific antibodies in antihuman serum and that the precipitates occupy the same position in immunoelectrophoretic patterns of the cerebrospinal fluid and of the serum. This suggests that both of the lipoprotein fractions in the cerebrospinal fluid originate from the serum.

This lack of any demonstrable immunoelectrophoretic difference between the lipoproteins in the cerebrospinal fluid and serum does not absolutely exclude the possibility of a difference in the composition of the lipids. The linkage between the lipids and the proteins is weak, and it is possible that the large lipid component bound to the β-globulins—the lipid portion of this lipoprotein represents about 70% of the complex—becomes detached on passage of this lipoprotein from the blood to the cerebrospinal fluid. The protein component—thus the minor portion of the lipoprotein—would then be able to continue through the barrier between the blood and the cerebrospinal fluid and, on the cerebrospinal fluid side, be linked to lipids emanating from the central nervous system. The cerebrospinal fluid and serum could then have the same protein component but a different lipid component.

This line of thought may be supported by the fact that the antigenic properties of the lipoproteins dwell in the protein component and that it would thus not necessarily be possible to separate two lipoproteins by immunoelectrophoresis if the protein components were identical. The one case in the present material in which lipids were bound to the γ-globulin in the cerebrospinal fluid but not in the serum

shows that lipoproteins in the cerebrospinal fluid may differ considerably from those in the serum. A preliminary gas chromatographic study of the fatty acid profile of cerebrospinal fluid also showed differences between the fluid and serum and might therefore also suggest that the fatty acids in the fluid were not of the same origin as those in the serum.[11]

On the other hand, the molecular weight of the protein component in the β-lipoprotein fraction is only slightly higher than that of the total α_1-lipoprotein complex. The α_1-fraction was regularly demonstrated even in the absence of any neurologic disorder and therefore irrespective of any change in the passage of proteins from the blood to the cerebrospinal fluid. Neither did subjects with or without neurologic disease show any differences in the amount of α_1-lipoprotein fraction determined by paper electrophoresis. Thus, demonstration of the β-lipoprotein fraction in patients with neurologic diseases only speaks in favor of the entire β-fraction migrating from the blood to the cerebrospinal fluid.

As mentioned, the occurrence of a β-lipoprotein fraction in the cerebrospinal fluid is a sign of neurologic disorder. As is apparent from the present investigation, this lipoprotein evidently derives from the serum. Determination of the β-lipoprotein in the cerebrospinal fluid may therefore be of interest in the study of pathologic changes in the passage of proteins from the blood to the cerebrospinal fluid.

SUMMARY

Opinions differ on the origin of the lipoproteins in the cerebrospinal fluid. In an attempt to elucidate this question, 59 cerebrospinal fluid samples from patients with and without neurologic disorders were studied by micro-immunoelectrophoresis for the presence of lipoproteins. No immunologic difference was found between the serum and the cerebrospinal fluid with respect to α_1-lipoprotein, which was demonstrated in all cases, and the β-lipoprotein, which was only demonstrable in the presence of neurologic disorders. These lipoproteins thus appear to originate from the serum and not from nervous tissue.

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Demonstration of large blood protiens in cerebrospinal fluid

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THE ORIGIN of the proteins in the cerebrospinal fluid is still conjectural. The electrophoretic mobility of these proteins when studied with paper electrophoresis does not differ from that of serum proteins. In addition, the cerebrospinal fluid proteins are usually precipitated by antihuman serum, which also suggests that they are identical with the serum proteins.

On the other hand, in some respects, the proteins in cerebrospinal fluid differ from those in blood. The normal fluid protein pattern will thus show 1 or 2 prealbumin fractions and a β_2-fraction, which are not found in the serum by usual paper electrophoresis. The β_1-globulin fraction is rather large and the γ-globulin fraction relatively low in the cerebrospinal fluid in comparison with serum. Furthermore, by immunoelectrophoresis, the transferrin is found to have a different appearance in the cerebrospinal fluid.[1, 2]

The protein pattern of pathologic cerebrospinal fluid sometimes resembles that of serum very much, and increased diffusion of blood proteins into the cerebrospinal spaces then may be assumed. This resemblance of the electrophoretic curve for fluid proteins with serum proteins may not entirely be due to diffusion of proteins into the central nervous system. Thus, Frick and Scheid-Seydel,[3] who used labeled proteins, showed that proteins may be synthetized within the central nervous system.

Therefore, the possibility of demonstrating or excluding the presence of large molecules of normal blood proteins—which because of their size and molecular complexity per se can be excluded as being of central nervous origin—in the cerebrospinal fluid may be valuable. Microimmunoelectrophoresis, which requires only very small amounts of protein sample, permits serial analysis of a given specimen with special antisera and staining methods.

This paper is concerned with the occurrence and diagnostic value of diffusion of large normal blood proteins into the cerebrospinal fluid. The fluid was studied for the presence of the following 4 blood proteins:

1. α_1-lipoprotein is an ellipsoid-spherical molecule with a molecular weight of 200,000. Its appearance in the cerebrospinal fluid has been discussed in a previous paper.[4]

2. α_2-macroglobulin was isolated by Schultze and associates[5] in 1955. It appears that the cerebrospinal fluid has hitherto not been studied for this protein. It is a spherical glycoprotein with a molecular weight of 846,000. On paper electrophoresis, this protein migrates as an α_2-globulin.

3. β-lipoprotein is a spherical molecule with a molecular weight of 1,300,000. The occurrence in the cerebrospinal fluid of this component has been discussed in the above-mentioned paper.[4]

4. Fibrinogen has a cross-sectional diameter of 38 Å and a length of 700 Å. It is thus a very long ellipsoid molecule. Its molecular weight is 330,000. Fibrinogen has been demonstrated also in cerebrospinal fluid samples without any clotting web.[6]

MATERIAL AND METHODS

The material consisted of cerebrospinal fluid samples from 5 patients with epilepsy, 12 with cerebral or spinal tumor, 10 with multiple sclerosis, 2 with meningitis, and 15 with no signs of neurologic disease. Most of the samples were obtained by lumbar puncture and the remainder by cisternal puncture.

No samples with an admixture of blood were accepted. In order to avoid admixture of ser-

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um, the first few drops of cerebrospinal fluid were discarded. The fluid was centrifugated for twenty minutes immediately after collection, and the cell-free supernatant was removed. The fluid was concentrated according to Mies[7] by dialysis in collodion bags (Membranfiltergesellschaft, Göttingen, Germany) under negative pressure for three to four hours.

The fractions were separated by microimmunoelectrophoresis according to a modified technic of Scheidegger,[8] described in detail elsewhere.[9] The α_1- and β-lipoproteins were obtained with antihuman serum and colored with Sudan black.[10,11] The α_2-macroglobulin and fibrinogen were demonstrated with specific antisera. These slides were stained with amido black 10 B. The agar (Reinagar) and antisera (rabbit) used were supplied by Behringwerke, Marburg/Lahn, Germany.

The total protein content of the original cerebrospinal fluid as well as of the fluid concentrate was determined by a slight modification[12] of a spectrophotometric technic suggested by Waddell.[13]

RESULTS

When antihuman serum was used for microimmunoelectrophoresis, a number of precipitation lines appeared (see figure, a). The precipitation lines of α_2-macroglobulin and α_1- and β-lipoproteins are marked. Demonstration of fibrinogen requires the use of antifibrinogen serum. When anti-α_2-macroglobulin serum was used, a selective precipitation was obtained (see figure, b).

In the present series of 44 cerebrospinal fluid samples, α_2-macroglobulin precipitation was found in 37 cases after diffusion against anti-α_2-macroglobulin serum. The precipitation line was sharp in 8 and weak in 29. In the remaining 7 samples, no precipitation was found against anti-α_2-macroglobulin serum.

Table 1 shows the correlation between these 3 types of findings and the clinical diagnoses. Sharply outlined α_2-macroglobulin fractions were only seen in the presence of neurologic disease (that is, in this study, cases of tumor in the central nervous system, multiple sclerosis, and meningitis). Some of these patients were also represented in the group with a weak or no α_2-macroglobulin fraction.

Table 2 summarizes the cerebrospinal fluid samples studied for the presence of α_1-lipoprotein, α_2-macroglobulin, β-lipoprotein, and fibrinogen, the separate proteins being arranged according to their electrophoretic mobility. The protein most commonly found in the cerebrospinal fluid was α_1-lipoprotein. This protein was found in all samples including those from the 15 persons without signs of neurologic disease. The next protein in order of frequency was α_2-macroglobulin and then β-lipoprotein and fibrinogen.

The 8 cerebrospinal fluid samples with a well defined α_2-macroglobulin fraction showed β-lipoprotein and/or fibrinogen. The 29 sam-

Microimmunoelectrophoresis with antihuman serum [a] and anti-alpha$_2$-macroglobulin serum [b] of cerebrospinal fluid from a patient with cerebral tumor. Slides are stained with amido black 10 B.

TABLE 1

CLASSIFICATION OF 44 CEREBROSPINAL FLUID SAMPLES ACCORDING TO DIAGNOSIS AND APPEARANCE OF ALPHA$_2$-MACROGLOBULIN PRECIPITATION LINE

Diagnosis	*Precipitation line of alpha$_2$-macroglobulin*			
	Sharp	*Weak*	*No*	*Total*
No neurologic signs	0	13	2	15
Epilepsy	0	4	1	5
Tumors in central nervous system	5	6	1	12
Multiple sclerosis	1	6	3	10
Meningitis	2	0	0	2
Total	8	29	7	44

ples with a weak α_2-macroglobulin fraction showed a β-lipoprotein fraction in 5 cases but never any fibrinogen. β-lipoprotein or fibrinogen was never demonstrable in the fluid samples unless α_2-macroglobulin was also found.

β-lipoprotein was found in 8 of the 12 cases of tumor in the central nervous system, and, in 4 of them, fibrinogen was also seen. Cerebrospinal fluid samples from the 2 patients with meningitis showed β-lipoprotein as well as fibrinogen. Only in 1 of the patients with multiple sclerosis was a β-lipoprotein fraction demonstrable and, in 1 case, fibrinogen. The cerebrospinal fluid of 1 patient with seizures contained β-lipoprotein. Neither β-lipoprotein nor fibrinogen was found in the 15 controls.

DISCUSSION

The 4 proteins studied originate from the blood. They are precipitated by specific antisera. The 3 fractions of relatively similar molecular appearance—α_1- and β-lipoproteins and α_2-macroglobulin—were demonstrated in the cerebrospinal fluid in a frequency related to their molecular weights.

Thus, α_1-lipoprotein (molecular weight, 200,000) was regularly found in both the presence and absence of neurologic disease and may thus be regarded as a normal cerebrospinal fluid constituent. The α_2-macroglobulin (molecular weight, 846,000) appeared to border the upper limit of the size of molecules normally capable of passing from the blood to the cerebrospinal fluid. On the other hand, the presence of this fraction in the fluid may perhaps also be a sign of some concealed disorder despite the fact that it was seen in samples from patients with no demonstrable neurologic disease, as also judged by the number of white cells, total protein, and paper electrophoretic

TABLE 2

NUMBER OF CEREBROSPINAL SAMPLES IN SEPARATE DIAGNOSTIC GROUPS IN RESPECT TO THE PRESENCE OF ALPHA$_1$-LIPOPROTEIN, ALPHA$_2$-MACROGLOBULIN, BETA-LIPOPROTEIN, AND FIBRINOGEN

Diagnosis	*Number of cases*	*Presence in cerebrospinal fluid of*			
		Alpha$_1$-lipoprotein	*Alpha$_2$-macroglobulin*	*Beta-lipoprotein*	*Fibrinogen*
No neurologic signs	15	15	13	0	0
Epilepsy	5	5	4	1	0
Tumors in central nervous system	12	12	11	8	4
Multiple sclerosis	10	10	7	1	1
Meningitis	2	2	2	2	2
Total	44	44	37	12	7

profile. Decision of this question, however, requires investigation of a larger series. In all of the cases in which the a_2-macroglobulin fraction was sharply defined, the patients had some known neurologic disease; also, the cerebrospinal fluid contained β-lipoprotein and/or fibrinogen, indicating an increased passage of proteins from the blood to cerebrospinal fluid.

Fibrinogen (molecular weight, 330,000) was relatively seldom found, even though its molecular weight is lower than those of a_2-macroglobulin and β-lipoprotein. This may possibly be explained by its different molecular structure. Thus, the passage from the blood to the cerebrospinal fluid may depend not only on the size of the molecule but also on its shape and perhaps also on other protein properties not studied in the present investigation. It thus seems that study of the cerebrospinal fluid for separate blood proteins may reveal the presence of a disorder in the passage between the blood and cerebrospinal fluid and hence also a neurologic disease.

The method might also add to our knowledge of the mechanisms involved in separate neurologic diseases. The frequency of β-lipoprotein and fibrinogen in the cerebrospinal fluid from patients with tumor of the central nervous system differed markedly from that observed in patients with multiple sclerosis. Both proteins were observed in the cerebrospinal fluid in two-thirds of the patients with tumor as against only one-fifth of those with multiple sclerosis. The passage from the blood to the cerebrospinal fluid thus appeared to be more frequently damaged with the former disease. Closer investigation of the heterogenous group of cerebral and spinal tumors in particular might yield further information. By investigating larger groups of patients with separate neurologic diseases and controls and possibly by extending the investigation to include other large blood protein molecules, it might be possible to devise a new clinical tool in the examination of the cerebrospinal fluid.

SUMMARY

Cerebrospinal fluid samples from 44 patients were studied by microimmunoelectrophoresis for the presence of a_1-lipoprotein, a_2-macroglobulin, β-lipoprotein, and fibrinogen. The frequency with which these components were demonstrated in the cerebrospinal fluid varied with their molecular weight and possibly also with the shape of the molecules. a_1-lipoprotein and a_2-macroglobulin could be demonstrated even in the absence of any neurologic disease. However, β-lipoprotein and fibrinogen were only found in cerebrospinal fluid samples from subjects with known neurologic disease. Demonstration of blood proteins of macromolecular type in the cerebrospinal fluid by microimmunoelectrophoresis may yield valuable information in the diagnosis of neurologic diseases with involvement of the passage of the proteins between the blood and the cerebrospinal fluid. An attempt is made to grade neurologic disorders with the aid of such determinations, hoping to find a sensitive supplementary tool in the examination of the cerebrospinal fluid.

This study is part of an investigation supported by the Swedish Cancer Research Council The authors are greatly indebted to Mr. and Mrs. Nils Edström for valuable help throughout this investigation.

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Primary reading epilepsy

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CERTAIN PATIENTS experience epileptic attacks only under particular circumstances. Those whose seizures can be predictably evoked by specific forms of repetitive afferent stimuli are of special interest. "Photogenic epilepsy" is probably the best known of these conditions, and other patients whose seizures are precipitated by listening to music have been reported.[1] Primary reading epilepsy is a third such syndrome.

In 1956, Bickford[2] described 6 patients who complained of a sensation of clicking in the jaw or of sudden jaw movement during prolonged reading. If they continued to read after these symptoms developed, they were liable to sudden loss of consciousness and a grand mal seizure. If they stopped reading as soon as the jaw symptoms developed, the major seizure did not ensue. This jaw-clicking syndrome was provoked in 5 of the 6 patients by having them read for long periods. The development of these symptoms coincided with the appearance in the electroencephalogram of a 3- to 6-cps paroxysmal discharge which was bilaterally synchronous and maximal in the parietal and occipital areas. Bickford suggested the term "primary reading epilepsy" to describe the clinical syndrome and to contrast these patients with those suffering from "a more general epileptic disorder" whose seizures were sometimes precipitated by reading.

Several papers on reading epilepsy[3–5] have subsequently appeared, but only a few of the cases described fall into the category of primary reading epilepsy. These include Stevens'[4] Case 3, Critchley's[5] Case 2, and possibly the 3 patients reported by Bingel.[3] We wish to record the clinical features of 2 further cases of primary reading epilepsy and to speculate on the pathogenesis of this syndrome.

CASE REPORTS

Case 1. W. N., a 19-year-old university student, was seen in April 1960. He first noticed involuntary jaw movements while reading during the autumn of 1959. These invariably occurred after he read aloud for five to ten minutes and after a longer period of silent reading. He described an involuntary opening of the jaw, sometimes associated with a snapping sound, and a tendency to keep repeating a syllable of the word he was attempting to pronounce. If he persisted in his attempt to read, these movements became very frequent and would finally totally disrupt his reading. If he rested for a few minutes, he could again read aloud for several minutes before they recurred. These symptoms were worse when the patient was fatigued or under emotional tension, and he finally sought medical help because of their increasing frequency before his spring examinations. He had never experienced these movements while writing or during spontaneous speech but was concerned that they might begin to interfere with conversational activities.

Also, since the fall of 1959, he had noted similar but much less worrisome sudden, involuntary movements in other muscles. While sitting quietly, he would often notice brief, repetitive twitches of muscles in the periorbital region or in an extremity. He had also become liable to "drowsing jerks" which were more likely to occur if he was startled "by a sound or a thought" while falling asleep.

There was neither a personal nor a family history of seizures. As far as the patient was aware, he had never lost consciousness nor suffered significant head trauma or central nervous system infection.

During the summer of 1959, a laceration on his lower lip inflicted by a dental probe became infected and marked edema, redness, and pain in the lip and lower face developed. He received 20 injections of penicillin as treatment for this infection, after which a generalized pruritis associated with erythematous skin lesions developed. This pruritis subsided very slowly over a period of many months and still bothered the patient from time to time.

He was an alert, cooperative young man of average intelligence and appropriately concerned regarding his symptoms. Conversational speech was normal. No significant abnormalities could be demonstrated on general physical and neurologic examinations.

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An electroencephalogram was recorded with the patient resting and while he was reading silently and aloud. The background activity in the resting portion of the record was stable. Alpha appeared at 10 cps, was well modulated and maintained, and showed a normal response to eye opening and closing (Fig. 1). No significant dysrhythmic activity appeared during five minutes of hyperventilation. Photic stimulation at 5 to 20 cps resulted in occipital driving bilaterally but did not precipitate epileptic or myoclonic activity.

After five minutes of silent reading, random low-voltage sharp waves appeared in the temporal leads of both hemispheres. After nine minutes of silent reading, moderate voltage spikes followed by irregular slow waves appeared in the right temporal lead. Similar activity but of lower voltage appeared in other leads from both hemispheres (Fig. 2). This abnormal electroencephalographic activity was associated with sudden, low-amplitude opening movements of the jaw, and the patient stopped reading for several seconds. Although he continued to read silently for another half hour, no similar electroencephalographic abnormalities appeared.

After he had read aloud for one minute, clear-cut hesitations in speech occurred. These were accompanied by, and probably due to, sudden opening movements of the jaw. Repeated attempts to pronounce a word resulted in recurrence of the jaw-opening movements, and the same syllable would be repeated several times. Finally, the entire word would be pronounced, and reading would continue. These involuntary jaw movements were associated with the appearance of high-voltage multiphasic spikes from the right temporal electroencephalographic leads (Fig. 3). It was at first believed that these spikes reflected true epileptic activity. However, after consultation with others,[6] we now feel that they represent muscle artifact and that no true electroencephalographic abnormalities developed during the period when jaw-opening movements were occuring.

When interviewed an hour after the electroencephalographic recording, the patient commented that he felt "tired and depressed." This he said was his usual reaction after any attempt to read aloud in public.

This patient received 300 mg. of Dilantin daily for four months without appreciable benefit. In September 1960, his anticonvulsants were discontinued and he was given 400 mg. of meprobamate three times a day. Shortly thereafter, his involuntary jaw movements began to decrease in frequency. Latterly, his medications have been discontinued without any exacerbation of his jaw-opening syndrome. It is our impression that this syndrome is subsiding spontaneously.

Case 2. V.S. was a 15-year-old student when he was seen in November 1956. In June 1956, while sitting reading, he suddenly felt his jaw pull open; then he was aware that his limbs were stiffening in extension, and he lost consciousness. He was alone at the time and did not know how long he was unconscious. On awakening, he felt "dizzy" and found that he had bitten his tongue. He felt well enough to go to school within an hour of this incident.

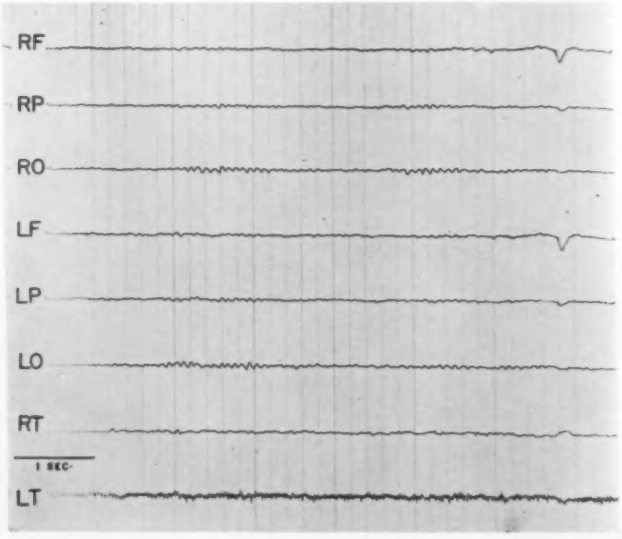

Fig. 1. Electroencephalogram recorded while patient rested quietly. Speed, 30 mm. per second

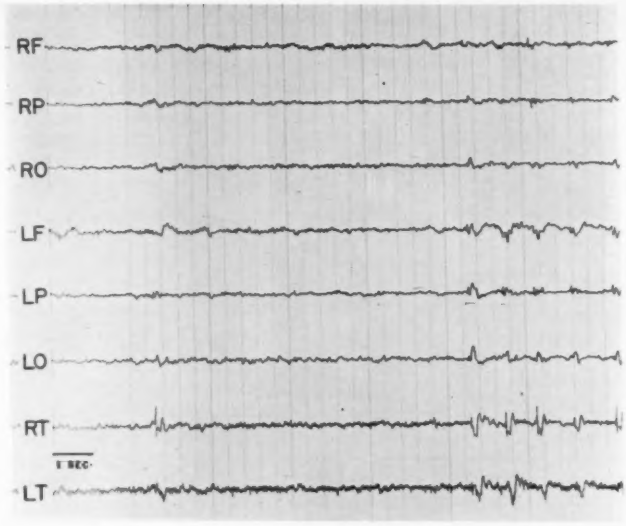

Fig. 2. Electroencephalogram after patient read silently for nine minutes. Speed, 15 mm. per second

The patient had no further symptoms until October 1956, when he contracted an upper respiratory infection which kept him home from school. While lying on his bed and reading, he suddenly noted that his jaw was pulling open and his eyes were beginning to water. He stopped reading for a few minutes and these symptoms disappeared. When he started to read again, these same symptoms recurred, environmental sounds became distant and indistinct, and his limbs stiffened; he was aware that he was making strange noises. He then lost consciousness. He was seen at this stage by his mother. The patient was unconscious and lying with his spine arched backwards and his limbs rigidly extended. No clonic movements were seen, but he was making

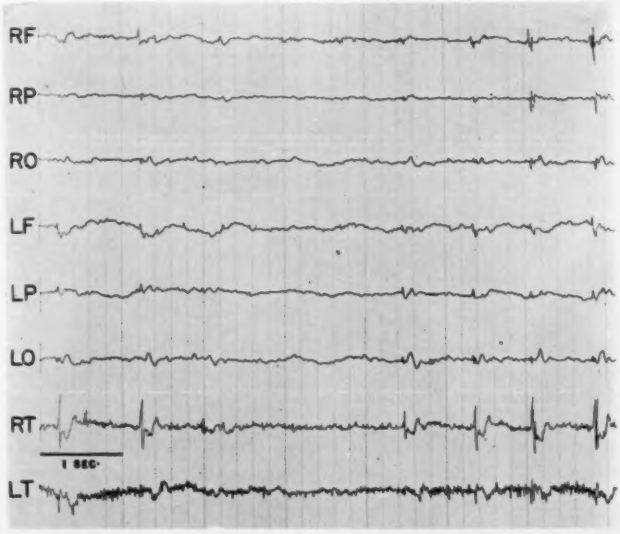

Fig. 3. Electroencephalogram after patient read aloud for one minute. Speed, 30 mm. per second

repetitive noises. After several minutes, his limbs relaxed and he slowly regained consciousness. For several minutes, he seemed confused, began to cry, and complained of difficulty in seeing. Some fifteen minutes after he recovered consciousness, his behavior was normal.

The patient had not experienced any seizures before 1956, and there was no family history of seizures. When 4 years old, he had been hit on the top of his head with a stone. His scalp had been lacerated, but he had not lost consciousness and there were no evident sequelae. At 12 years of age, he was in hospital for investigation of abdominal pain. No definite diagnosis was made, and the symptoms disappeared spontaneously.

He appeared an alert, intelligent boy whose general physical and neurologic examinations were completely normal.

An electroencephalogram was recorded. During periods of rest, the background activity was stable. Alpha appeared at 10 cps, was well modulated, and showed the normal response to eye opening and eye closing. After two minutes of hyperventilation, short bursts of 4- to 5-cps theta appeared from all leads of both hemispheres. Photic stimulation did not provoke significant dysrhythmia.

During fifteen minutes of silent reading, the electroencephalographic activity was composed mainly of moderate voltage, 5- to 7-cps theta waves. No clear-cut paroxysmal activity or spike discharges were noted. The recording was considered to be within normal limits.

This patient received 300 mg. of Dilantin daily for eighteen months, and his anticonvulsants were then stopped. No further seizures have occurred.

DISCUSSION

Any hypothesis concerning the pathogenesis of primary reading epilepsy must explain how the act of reading might evoke myoclonus and generalized seizures in susceptible persons. That repetitive afferent stimuli set up during reading play an important role has been assumed. The nature of these afferent stimuli remains in doubt, but there are two major possibilities which may be important.

During reading, the eyes do not move steadily along the lines of print but in short, rapid, so-called "saccadic" movements with brief episodes of fixation between them. According to Adler,[7] each saccadic movement occupies 0.02 to 0.03 seconds and each fixational pause lasts 0.2 to 0.3 seconds. Since no vision is possible during the saccadic movement, reading, in effect, results in rapid, intermittent visual stimuli. This has led some authors to suggest that these discontinuous and rapidly repetitive visual stimuli precipitate epilepsy in the same way that rapid, intermittent photic stimuli precipitate myoclonic jerks or seizures in light-sensitive persons.

An alternative and, to us, more attractive hypothesis would emphasize the role of proprioceptive impulses originating in extraocular, facial, and masticatory muscles during reading. There is a considerable controversy in the literature regarding the presence of afferent fibers in the ocular motor nerves of man. However, it is accepted that afferent receptor organs in the form of muscle spindles and tendon organs can be demonstrated in the extraocular muscles.[8] Cell bodies resembling those of the mesencephalic nuclei of the trigeminal complex may occasionally be demonstrated in the oculomotor, trochlear, and abducens nuclei—or less commonly along the intramedullary course of the ocular nerve fibers.[9] The presence of such cell bodies in these sites suggests that they give origin to afferent processes which travel in the ocular motor nerves. Further, the microscopic appearance of these cells suggests that they are displaced cells of the mesencephalic trigeminal nuclei. These nuclei are elongated structures which extend from the level of midpons caudally to the level of the posterior commissure orally. The cell bodies composing these nuclei are numerous at the midpontine level, where they give origin to proprioceptive fibers coursing in the trigeminal and facial nerves. In the oral portions of the pons, the cells are few in number but again become numerous in the midbrain. All of this is presumptive evidence that, in man, proprioceptive impulses proceed from the extraocular muscles to the brain stem via afferent fibers in the oculomotor, trochlear, and abducens nerves and that the cell bodies of these fibers constitute the oral portions of the mesencephalic trigeminal nuclei.

It is thus probable that, during silent reading, the cell bodies of the oral portions of the mesencephalic trigeminal nuclei receive repetitive bursts of afferent proprioceptive impulses originating in the extraocular muscles of the eyes during saccadic movements. If the reading is done aloud, the more caudal parts of the same nuclei receive discontinuous bursts of proprioceptive impulses from the masticatory and facial muscles. Reading requiring concentration would presumably increase the

number of impulses originating from all of these muscle groups. It is suggested that these proprioceptive impulses, in addition to repetitive visual stimuli, may be important factors in the precipitation of myoclonic jerks and seizures during reading in susceptible persons.

Experimentally, repetitive afferent stimuli may give rise to abnormal neuronal activity, which is often epileptic in nature, if appropriate areas of the nervous system have been rendered "unstable" by mechanical, chemical, or biochemical means. Such repetitive afferent stimuli may cause abnormal neuronal activity in these areas by virtue of synaptic transmission or, possibly, by the field effects of ephaptic transmission.[10] If we apply these physiologic concepts to reading epilepsy, one must begin with the assumption that neuronal patterns of the brain stem are "unstable" in such patients. Repetitive proprioceptive stimuli might then provoke abnormal activity in the reticular formation and the motor trigeminal nuclei by virtue of the synaptic connections between the mesencephalic trigeminal nuclei and these structures. Such activity might well account for the myoclonic and tonic jaw movements which may develop during reading. An increase of the abnormal activity in the facilitatory portion of the reticular activating system might result in generalized myoclonic spasms, and, if repetitive synchronous discharges were set up, they might become self-perpetuating and result in a grand mal seizure.

The cause of the neuronal instability in the brain stem of patients with primary reading epilepsy remains even more obscure. We cannot assume that these patients do not have small focal lesions of the brain stem or cerebral hemispheres. However, there has been no clinical evidence of such fixed lesions, and it seems a reasonable assumption that the symptoms of primary reading epilepsy may appear in their absence. If a common anatomic or biochemical variation were responsible, one would expect the syndrome to run in families, but, in contrast to photogenic epilepsy, no familial incidence has been recorded. Finally, the possibility of an acquired but temporary pathophysiologic basis must be considered. Our first patient, for example, experienced generalized pruritus for several months before the motor phenomena associated with reading appeared. During this period, his brain stem reticular formation was presumably bombarded with impulses via collaterals from the exteroceptive sensory pathways traversing the brain stem. Is it possible that, during this period, abnormal synaptic relationships were developed or enhanced which rendered the neuronal systems in the reticular formation unstable?

Only further detailed study of these patients will prove or disprove the emphasis which we would place on brain stem mechanisms in the pathogenesis of primary reading epilepsy.

SUMMARY

Patients with primary reading epilepsy complain of a sensation of jaw snapping or jaw opening when reading. Such symptoms are most likely to develop when the patient reads aloud or when the reading material requires concentration. A generalized seizure is likely to occur if he persists in reading once the myoclonic jaw movements appear. These patients do not have seizures under any other circumstances, and their neurologic examinations are normal. Their electroencephalograms are normal during the resting state but may show diffuse paroxysmal activity when jaw-opening movements are provoked.

In this paper, the clinical features of two further cases of primary reading epilepsy have been described. We have speculated regarding the pathogenesis of the syndrome and emphasized the role which repetitive proprioceptive impulses may play.

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Vestibular nystagmus in newborn infants

A study by visual, photographic, and electrooculographic methods. Preliminary report

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with the assistance of Anne Bolesworth, Pamela Coues,
Ralph Glazier, and Mary Messitt

VESTIBULAR NYSTAGMUS in response to rotation has been variously reported to be absent[1–4] and present[5,6] in newborn and very young infants. The manual rotation technic of McGraw[6] has become a standard part of the neurologic examination of infants, but a trial of this maneuver in any newborn nursery will quickly disclose that a variety of responses are obtained. Some neonates show prompt and vigorous rotational and postrotational nystagmus, others show it only with difficulty and persistence, still others show tonic deviation of the eyes without nystagmus, and a few fail to show even this. In order that these differences might be correlated with the infants' past histories and existing states, a study was undertaken for more quantitative evaluation of the eye movements of newborn infants in response to rotation. For this purpose, efforts were made to adapt the electrooculographic technics discovered by Dewar,[7] developed by Schott[8] and Meyers,[9] and more recently reviewed by Marg.[10]

Fig. 1. View of electrically driven rotating table, set up for cinematographic recording. Electrooculograms are recorded from a multiple-lead cable suspended from the ceiling.

METHOD

Direct observations of eye movements in response to manual rotation were made with selected full-term infants and, their condition permitting, premature infants at the Boston Lying-In Hospital on repeated occasions. The same observer rechecked his own findings on different occasions, and, at other times, different examiners tested the same babies separately. The babies were either held vertically above and facing the examiner with their heads inclined 30° forward from the vertical or else held in the supine position in front of

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him with their heads toward him and inclined downward 60° from the horizontal. Either position places the horizontal semicircular canal approximately in the horizontal plane.

These direct observations were initially made only after maximal stimulation consisting of a snap to the baby's foot sufficiently painful to produce a sustained cry. Subsequently, similar observations were also made before (or with minimal) as well as after stimulation, with careful notation of the infant's state. To be considered "alert," the baby had to keep both eyes open, look about, and maintain tone throughout the period of testing; the opposite circumstances were required for him to be called "asleep." Otherwise, his state was considered "doubtful." Particular care was taken to avoid a difference in the rate of rotation and deceleration before and after stimulation.

Agitation, crying, or excessive movement such as stretching tended to suppress nystagmus. Persistence of these circumstances made testing unreliable, for which reason such observations were not included in our results. Sucking, on the other hand, made it easier to obtain and record nystagmus; a nipple was therefore routinely used to enhance these observations in the alert baby.

More detailed study was carried out with an electrically driven rotating table similar to that constructed by Laurence and Feind[11] for photographic recording, except that the infants were placed on the opposite arm of the table from the camera. Electrooculographic recordings were also made, and electroencephalograms and respirations were recorded.

The baby was placed with head tilted downward approximately 60° from the horizontal in a modified chair bed, mounted at one end of the rotating table, the axis of rotation being in the center of the table, at the opposite end of which was mounted a 16-mm. motion picture camera (Fig. 1). The table could be rotated in clockwise or counterclockwise direction at variable speeds and was fitted with an electric brake so that rotation could be stopped quickly and at a constant rate of deceleration. Speeds of 21, 16, 14, 11½, 10, and 8½ rpm were used.

All electrical recordings were made on a Type R Offner dynograph. These were of alternating current potentials; direct current methods require further study for their practical use.

For the eye movements, a time constant of 0.3 seconds was used, amplification varying between 5 and 10 μv per millimeter. Solder tip electrodes held in place by bentonite were placed, 1 as close to the outer canthus of each eye as possible and 1 on the glabella, recording being from the electrode at the outer canthus to the midline electrode.

Respirations were recorded with a Sanborn pneumotachygraph.

The electroencephalogram was recorded with a time constant of 0.3 seconds, amplification being 5 μv per millimeter. Solder tip electrodes held in place with bentonite were used, the electrode placings being frontal, central, and parietooccipital on each side. Bipolar recordings were made, frontal to central and central to parietooccipital.

Because the baby was not placed over the axis of rotation but at a distance from and facing it, his true rotation with respect to his own axis was opposite to his apparent direction of motion. Thus, he appeared to look ahead at the beginning of rotation and backward after stopping. The directions are summarized in Table 1.

TABLE 1

Direction of rotation	*Head position of baby*	*Rotation is to*		*True direction of baby's rotation*	*Rotational deviation, eyes to*		*Postrotational deviation, eyes to*	
		Viewer's	*Baby's apparent*		*Viewer's*	*Baby's*	*Viewer's*	*Baby's*
Clockwise	Upright	Right	Left	Right	Right	Left	Left	Right
Clockwise	Inverted	Right	Right	Left	Right	Right	Left	Left
Counterclockwise	Upright	Left	Right	Left	Left	Right	Right	Left
Counterclockwise	Inverted	Left	Left	Right	Left	Left	Right	Right

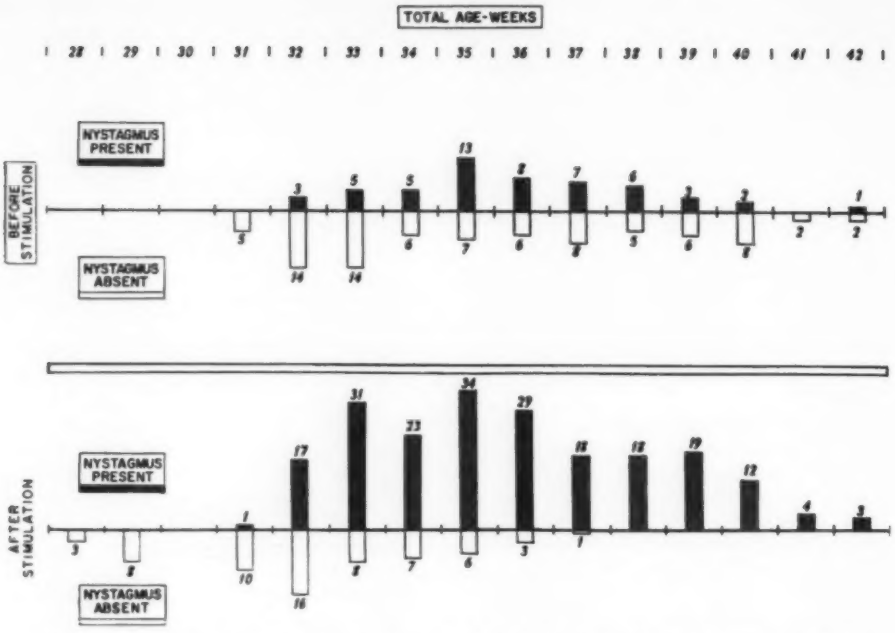
TOTAL AGE-WEEKS
28 29 30 31 32 33 34 35 36 37 38 39 40 41 42
NYSTAGMUS PRESENT
BEFORE STIMULATION
NYSTAGMUS ABSENT
3 14 5 14 5 6 13 7 8 8 7 8 6 5 3 6 2 8 1 2
NYSTAGMUS PRESENT
AFTER STIMULATION
NYSTAGMUS ABSENT
3 8 1 10 17 16 31 8 23 7 34 6 29 3 18 1 18 19 12 4 3

Fig. 2. Relationship of postrotational nystagmus (on direct observation) to maturity before and after stimulation. Length of bars represents number of babies tested regardless of state. Note that, after stimulation, absence of nystagmus occurred only in infants of 37 or less weeks "total age" (gestational age plus extrauterine life).

RESULTS

During the course of this study, it became evident that, by direct observation, nystagmus is more easily and uniformly observed after rather than during rotation. The results noted in Figures 2 and 3 thus relate to postrotational nystagmus, which was seen in all babies except one that could be considered "alert." It is evident that stimulation may be required to produce alertness. By electrical recording, however, nystagmus can be studied in much more detail both during and after rotation. Figure 4 shows successful recordings from an alert baby being rotated clockwise. At the start of rotation, the eyes deviate to the baby's left (downward in the tracing), with the quick component of the nystagmus to his right (upward), the directions being reversed in postrotational nystagmus. Nystagmus begins at 3 to 4 beats per second, slowing to 2 and finally 1 or less before stopping. For these tracings, a speed of 21 rpm was used. Acceleration was by manual turning of a rheostat, as quickly as possible but not constant (actually, acceleration as slight as 0.2 to 0.3° per second has been reported sufficient to produce nystagmus[12]). Deceleration by cutting the current supply to the motor and applying the brake simultaneously with a single switch was at a constant rate, producing a full stop in one-fourth revolution. Figure 5 is a similar record of counterclockwise rotation.

The time intervals of the tracings are quite well duplicated from one trial to another with the same baby, on one or different occasions, as shown in Table 2.

The nystagmus began after a latent period of under a second after either acceleration or deceleration, and its duration varied slightly with the speed of rotation (for 4 turns in each instance) but was not obtained at less than 11 rpm (Table 3).

TABLE 2
REPEATED TRIALS WITH SAME NORMAL INFANT

Age	4 days	9 days
Number of trials	8	4
	Time in seconds	
Time, acceleration to onset of nystagmus	0.5 ± .04	0.7 ± 0.4
Duration, rotational nystagmus	8.5 ± 2.5	9.0 ± 1.5
Time, deceleration to onset of nystagmus	0.5 ± 0.3	0.8 ± 0.2
Duration, postrotational nystagmus	8.3 ± 3.2	3.3 ± 1.0

TABLE 3
EFFECT OF SPEED OF ROTATION

rpm	21	16	14	11.5	10
	Time in seconds				
Time, acceleration to onset of nystagmus	0.6	1.0	1.0	0.6	—
Duration, rotational nystagmus	8.7	8.5	6.0	5.0	0
Time, deceleration to onset of nystagmus	0.6	0.8	1.0	0.9	—
Duration, postrotational nystagmus	6.8	6.3	4.1	3.0	0

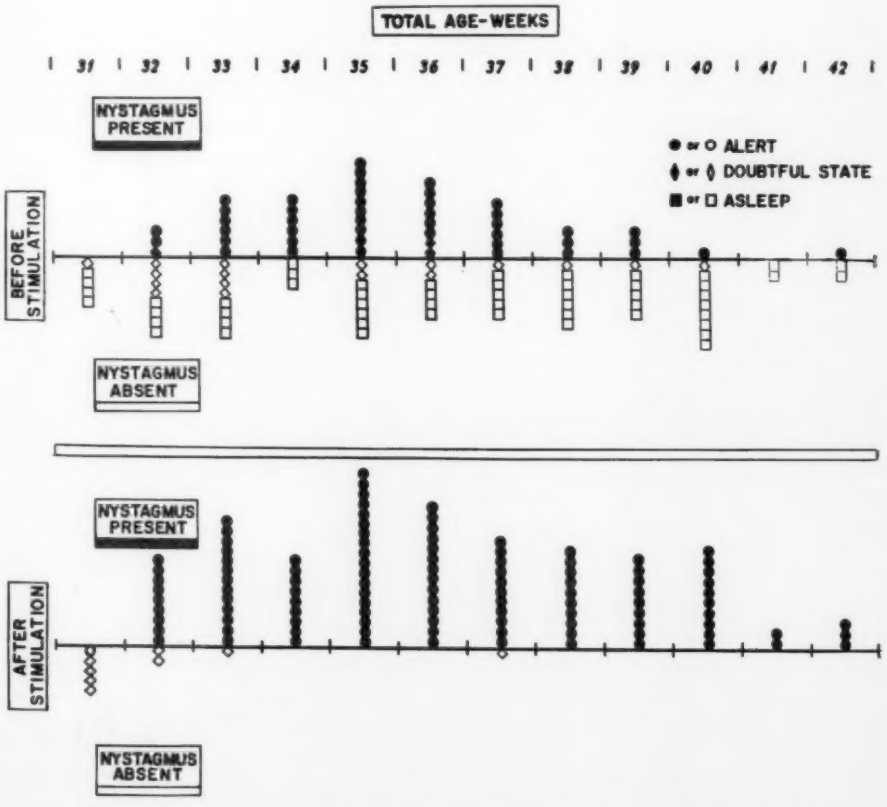

Fig. 3. Relationship of postrotational nystagmus (on direct observation) to state. Note that all alert babies but 1 had nystagmus and all sleeping babies did not regardless of "total age." Not included are a number of small premature infants lacking nystagmus in Figure 2, particularly after stimulation, as their state of wakefulness could not be accurately determined in many instances.

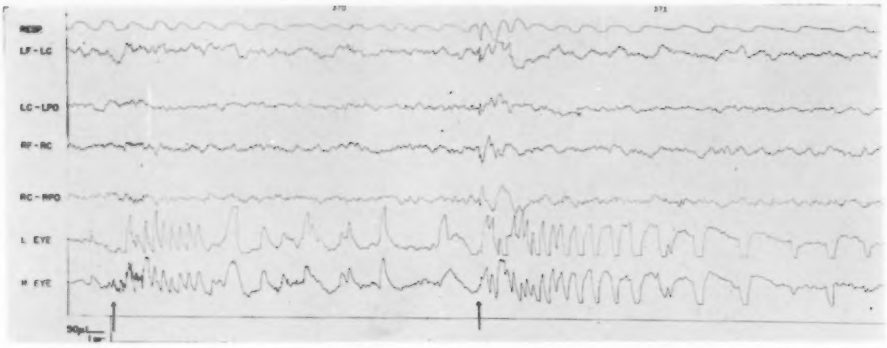

Fig. 4. Recording of respirations, electroencephalogram, and electrooculogram of an alert full-term baby, rotated clockwise. At start of rotation (first arrow), vestibular stimulation produces deviation of eyes to baby's left (downward on graph, with gentler slope) with quick recovery phase of nystagmus to right (upward, with steep, almost vertical slope). Initial deviation of eyes to left is gradual and obscured in tracings of alternating current potentials, so that first visible spike is of the quick phase of the nystagmus, steeply upward. Nystagmus soon slows after rotation as steady speed is reached. After rapid deceleration (at second arrow), similar phenomena occur, with direction reversed.

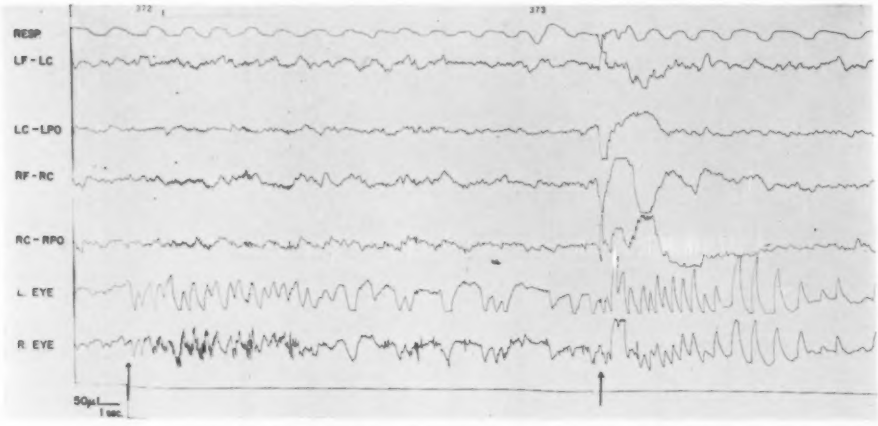

Fig. 5. Counterclockwise rotation. Directions all reversed from Figure 4

The nystagmus was not altered by covering the eyes or by momentarily blinding the baby with a flash of light; this indicates that he is not dependent on visual cues or attempts at fixation and is consistent with the reports of others with adults.[13–16] Nystagmus may even be intensified by covering the eyes or closing them,[13–16] even in blind persons.[17]

Situations in which nystagmus was depressed or absent were:

1. Sleep. (Figs. 2, 3, 6, and 7). Nystagmus was unobtainable when there was evidence of sleep by observation, electroencephalogram, and regular, slow respirations (one of the most sensitive criteria in newborn infants) but was also missing in some infants who appeared only slightly drowsy, with waking-type electroencephalograms and respiratory patterns. Its loss appears thus to be one of the earliest and most sensitive indications of approaching

sleep. **Recent feeding** also made it more difficult to obtain nystagmus; in this situation, the response appeared to relate directly to the state of wakefulness or sleep.

2. Prematurity. Our initial clinical impression was that only forced deviation of the eyes, without nystagmus, was to be obtained in the majority of the smaller premature infants (Fig. 2. However, this proved to reflect in most instances greater difficulty in getting the smaller babies well awake; if thoroughly alert, all premature infants but one showed nystagmus similar to that in full-term infants (Fig. 3).

Serial observations on a few smaller premature infants showed the appearance of nystagmus with increasing age, at a total age of about 33 weeks (Fig. 8).

Other circumstances which appeared to depress or abolish nystagmus in our clinical experience were:

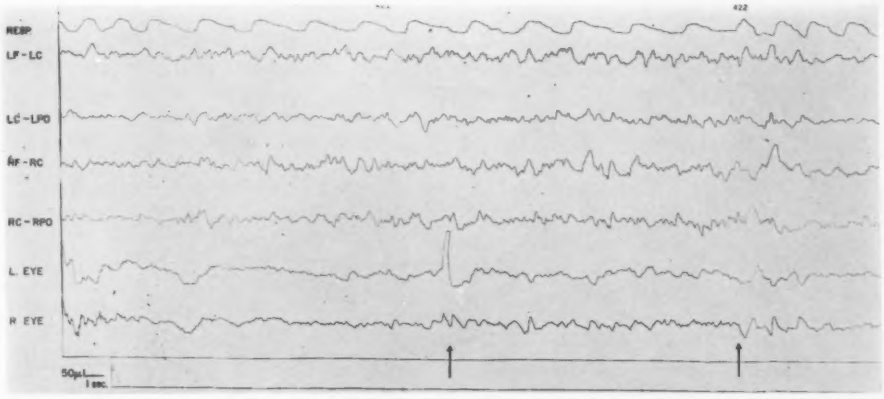

Fig. 6. Deep sleep with slow, regular respiratory tracing and sleep pattern in electroencephalogram. No definite rotational or postrotational nystagmus obtained

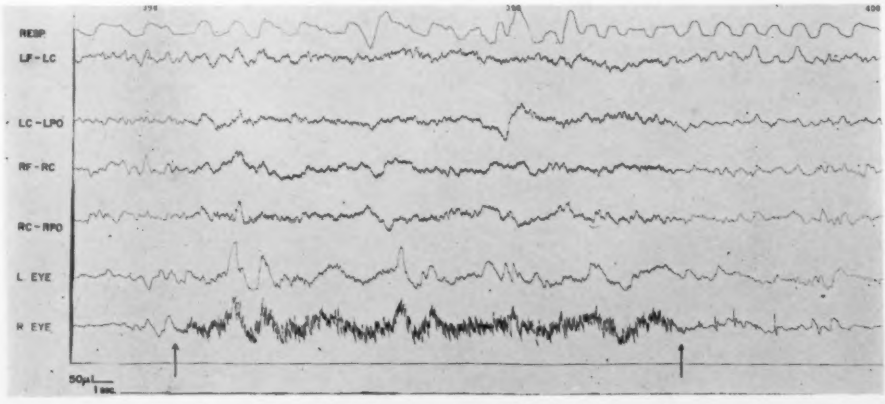

Fig. 7. Recordings from baby who had eyes open but looked drowsy rather than alert. Respirations were suggestive of approaching but not actual sleep, and electroencephalogram was of the pattern seen in neonatal infants when awake. Nystagmus was not obtained, however, and its disappearance is usually one of the earliest indications of approaching sleep.

3. Heavy maternal anesthesia in the case of babies tested in the first forty-eight hours of life. This is consistent with the reports of others concerning the effect of drugs on nystagmus in adults,[18–20] although it has been noted that barbiturate poisoning may produce spontaneous nystagmus.[20]

4. Anoxic or traumatic births, especially if accompanied by other signs of general depression of central nervous system function.

5. Marked hyperbilirubinemia. It appears that the common denominator of factors 1 through 5 is an alteration in the state of consciousness, although it is conceivable that some, especially hyperbilirubinemia, may have a direct effect on eye movement. Such alterations can abolish the quick phase of rotational or postrotational nystagmus in infants, leaving only forced deviation of the eyes, even if relatively slight in degree, while comparable effects in adults are reported only with much more extreme changes.[21–23] Further, vigorous efforts to awaken such babies by painful stimuli, followed by pacifying them with a sugar nipple in the mouth, were if successful almost always followed by prompt and vigorous nystagmus on repeated trial.

In 6 babies, not even forced deviation of the eyes was obtainable in response to rotational testing. The clinical histories were as follows: 3 cases, prolonged streptomycin therapy; 1 case, kernicterus, confirmed at autopsy; 1 case, neonatal convulsion, unknown cause, suspected kernicterus; 1 case, severe subarachnoid hemorrhage.

In many instances, the same babies were tested for opticokinetic nystagmus by the method of Gorman, Cogan, and Gellis.[24] In full-term infants, this response was almost always obtainable or not in the same approximate degree as the vestibular nystagmus, although the two responses are probably sub-

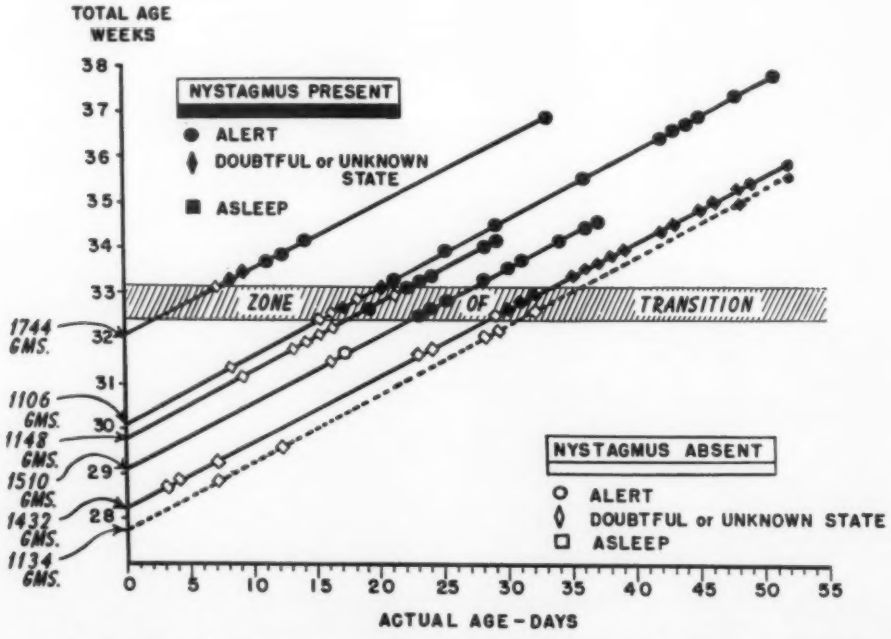

Fig. 8. Postrotational nystagmus (on direct observation) after maximal stimulation in 6 serially followed premature infants. Note that its appearance relates to the total age (about 33 weeks) rather than to either the gestational age or actual age alone. Figures in grams at left are birth weights.

served by quite different pathways.[25] The clinical discrepancy is that opticokinetic nystagmus is much more difficult and frequently impossible to obtain in the smaller premature infants (under 3½ lb.).

It would clearly be desirable to study nystagmus in response to caloric stimulation of the same babies, although one would expect the results to be quite similar to those in the case of rotational stimulation. (Actually, the caloric response has been variously reported as present[26] or absent[27,28] in newborn infants.) Further study in this respect is complicated by technical difficulties such as the presence of vernix caseosa in the auditory canals.

DISCUSSION

While rotational or postrotational nystagmus can be obtained in both premature and mature infants much as in adults, the implications of this are obscure with respect to both the anatomic pathway of the response and the degree of function of the various levels of the central nervous system in early infancy. The normal nervous pathway is uncertain with respect to the quick component of the nystagmus,[29] and reported data are conflicting. In lower animals, brain-stem mechanisms have been stated to be sufficient[30–32] but the response is at least modifiable by hemidecerebration.[33] A similar integrity of opticokinetic nystagmus in decerebrate animals has been repeatedly described but may be chiefly due to the localization of considerable visual function in tectal areas. Caution in attempting to apply results of animal experiments to man is indicated in the case of both opticokinetic and vestibular nystagmus.

In man, abnormalities of vestibular nystagmus (chiefly to caloric testing) have been well-documented in the presence of cerebral lesions.[22,34–36] It has also been suggested that the response may be based on a mechanism at brain-stem level but capable of modification (directional preponderance) by lesions at a higher level.[37] The presence of the response, as well as that of opticokinetic nystagmus, in neonates may argue for the latter view, if one adheres to the traditional belief that they have little or no cerebral cortical activity. Quite possibly, however, a lower-level embryonal mechanism may be involved in earliest infancy, to be superseded or largely controlled by a higher one later on. The situation may be similar to that of focal motor seizures, which are not necessarily of cortical origin in the newborn and have even been described in anencephalics.[38] Further work in this field of neonatal neurophyiology is clearly needed.

SUMMARY

1. The response of the eyes to vestibular stimulation by rotation has been tested in normal and abnormal full-term newborn and premature infants. Electrooculographic and photographic methods have been utilized, as well as direct observation. An electrically driven table provided constant rates of rotation and deceleration.

2. Rotational and postrotational nystagmus quite similar to that seen in adults should be obtainable in all normal full-term infants and in the larger normal premature infants. However, considerable care is required to get the baby thoroughly awake.

3. Only tonic deviation of the eyes without the quick component of the nystagmus may be obtained if the infant is sleepy, recently fed, markedly jaundiced, or very premature or has had an anoxic or traumatic birth or if its mother was heavily anesthetized. The common denominator of these factors appears almost always to be some alteration of the state of consciousness, of which the absence of vestibular nystagmus under proper conditions seems one of the most sensitive signs in the newborn. It changes earlier with approaching sleep than do electroencephalographic tracings or respiratory rates and rhythms and is a useful tool for physiologic investigations.

4. No response (not even forced deviation) to rotation was obtained in 6 infants, and this appears to be a sign of grave abnormality of the nervous system; 3 babies had had prolonged streptomycin therapy, 1 had kernicterus (confirmed by autopsy), 1 had convulsions and other signs of abnormal central nervous system function, and 1 had severe intracranial hemorrhage.

5. Testing for rotational nystagmus by the simple manual method is a useful part of the clinical neurologic examination of newborn infants, applicable in either the delivery room

or nurseries. If abnormal, it is a valuable clue to the existence of depressed function of the central nervous system and an addition to the limited number of criteria available at this age. The maneuver also makes immediately obvious the external rectus paralyses which occur by no means rarely in the newborn.

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Neurology

BOOK REVIEWS

Fallout: A Study of Superbombs, Strontium 90 and Survival

edited by John M. Fowler, 235 pp., ill., Basic Books, Inc., New York City, 1960. $5.50

The controversial nature of the subject of this book and the fact that it has only slight relevance to neurology makes a review somewhat more difficult than usual. The book contains a foreward by Adlai Stevenson and 12 chapters by 11 contributors in the fields of physics, meteorology, genetics, biophysics, biochemistry, and civil defense, plus a 30-page appendix and glossary on some necessary background information. The chapter headings in order are Bombs and Their Products; The Global Pattern of Fallout; From Bomb to Man (that is, the ways in which fission products reach the human subject); The Rising Level of Fallout; Biological Effects of Radiation; Radiation and Future Generations; Radiation Accidents; Protection and Treatment; Civil Defense; Detection of Bomb Tests; Nuclear War; and National Survival.

This book covers more than just the facts of these various matters. Opinions, policies, and philosophies are woven into many of the presentations, and it is obvious that honest but emotional points of view color some of the discussions. A reviewer's or reader's reaction to this book will inevitably be colored in an analogous fashion. This reviewer has for various reasons been exposed in some detail to most of the information contained in this book longer than most of the reading public, so that it is a more familiar, less emotionally charged subject than it might otherwise be. As Adlai Stevenson puts it in the foreword, "Realities lose some of their terror when we face up to them, and an understanding of the technical aspects of our nuclear hazards gives us a more hopeful outlook on the possibilities for solutions."

Thus, it is no great surprise to the reviewer that the consensus derived from this book is that the long-term problem of fallout is not as ominous or as formidable as much of the daily press would suggest. For example, a most reasoned statement by Dr. Walter Guild (a Yale biophysicist) at the end of his chapter on Biological Effects of Radiation says:

"As I have pointed out, the uncertainties about these numbers (of radiation victims) are not important to the way I feel about fallout: the odds against damage are high enough so that I do not feel any special concern for the safety of my family or myself. Yet because the number of people seriously hurt is not zero, I feel I must ask whether the risks are justified. This takes us out of the area of science and into morals and politics in the broadest sense. One medium-sized war anywhere in the world in the next 50 years, or the failure to prevent one major famine, would easily do more damage to life than fallout will.

"The second thought is that fallout is not precisely the major issue with regard to the bomb tests. Behind this worry lies the much greater fear of nuclear war, and if we are truly concerned about war, then let us by all means use our wisdom in going after that subject directly."

Not all the contributors to this volume nor

all the readers share the same views or, perhaps better, give these matters the same relative emphasis. Hence, the reactions to this book must be widely varied, and no reviewer could say whether it is good, bad, or indifferent. The chapters are well and clearly written and, with few minor exceptions, are understandable to any informed reader. The above quotation will provide some concept of the conflict facing each contributor in presenting his subject and indicate that all is not fact pure and simple. To this reviewer, the book has managed to collect most of the basic information available and to present it in a readable fashion. If one is aware that the reading of it must be critical, at least where facts leave off and opinions enter, it should provide readers with a useful source for understanding the basis for much of our national and international controversy on the subject and for forming some opinions of their own.

D.B.T.

Der Liquor cerebrospinalis im Kindesalter

by Professor D. H. Schönenberg, 175 pp., Georg Thieme Verlag, Stuttgart, 1960. DM 29.

Studies on the cerebrospinal fluid in infancy and childhood are reviewed, and many personal observations are included in this monograph by Professor Schönenberg, the pediatrician-in-chief of the Aachen City Hospitals.

The book is divided into two parts. The most important section deals with the composition and methods of analysis of the fluid. It contains a brief account of the blood-brain barrier and of the experimental methods of testing its integrity. The chapter on electrophoretic studies of spinal fluid is of particular interest. Methods of chemical determination are reported in some detail, in particular those described in the European literature. An extensive table of normal values of many constituents of cerebrospinal fluid serum is reproduced from a German text.

The second section reviews the spinal fluid findings in pathologic states, with particular emphasis on bacterial infection of the meninges and brain. Findings in viral infection and noninfectious neurologic disease are very briefly discussed.

The book is intended primarily for the pediatrician, but it is apt to be more useful to the biochemist and clinical investigator.

A very extensive and well prepared list of references is included.

J.P.R.

Sir Geoffrey Jefferson—Selected Papers

by Sir Geoffrey Jefferson, 564 pp., ill., Charles C Thomas, Springfield, Ill., 1960. $22.

This is a collection of papers of Sir Geoffrey Jefferson, the dean of English neurosurgeons. In the foreward, Sir Geoffrey admits that the choice of papers for republication was difficult but that he gave preference to those papers which had been published some years previously. The papers are grouped in sections, the first being largely of a philosophic nature; the second, historical and biographic papers; the third, essays on neurologic surgery; and, finally, a paper on a recent visit to Russia.

Sir Geoffrey has declared that his specialty has to do with the master system of the body and that all other specialists—cardiac, gastrointestinal, renal, or endocrine—are kind of maintenance engineers whose function it is to keep the nervous system working smoothly and efficiently, he treats his subjects with the same exalted approach. Consequently, in this book, one may read Sir Geoffrey's many original contributions, written in a delightful style, on such subjects as tentorial pressure cone, cerebral aneurysms, visual field defects due to chiasmal lesions, and consciousness. The papers are illustrated with excellent photographs and drawings, some redrawn for this edition. Sir Geoffrey's postscripts appended to some of these papers are enlightening commentaries on the progress of brain surgery in the past few decades. The book has a good index.

Neurosurgeons will give a special welcome to this volume, for it brings together many fundamental contributions of one of the most outstanding surgical neurologists of our time. Other students of the nervous system may find in it much instructive and interesting clinical scientific knowledge presented in a pleasing and engaging literary style.

A.E.W.

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Contraindications:

1. Severe renal or hepatic damage.
2. Active intracranial bleeding.
3. Marked dehydration.

   Caution: Lower extremity infusion in older patients is recommended.

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

MAY 1961

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ANA Prepares for Atlantic City The American Neurological Association will hold its eighty-sixth annual meeting at the Claridge Hotel in Atlantic City June 12 through 14. The scientific sessions will be in the morning and afternoon, Monday, June 12, and Tuesday, June 13; there will be a morning session only on Wednesday, June 14. The annual banquet will be held on Tuesday, June 13. All inquiries and communications should be sent to Dr. Melvin D. Yahr, ANA Secretary, Neurological Institute, 710 West 168th Street, New York City 32.

Other Meetings in Atlantic City The American Association of Neuropathologists will begin their annual sessions on Saturday, June 10, two days before the ANA meeting, under the presidency of Richard Richter of Chicago. On Sunday, June 11, the Association of Neuropathologists and the ANA will hold a joint symposium with A. Earle Walker in the Chair. The symposium is divided into 3 parts: Molecular Transports Across Neural and Non-Neural Membranes, Membranes and Myelin, and Membranes and Synapses.... The American EEG Society will conduct its fifteenth annual meeting at the Hotel Claridge in Atlantic City June 8 through 11, 1961. A special feature of the meeting will be a symposium on memory. The program chairman is Frank Morrell, Division of Neurology, Stanford Medical Center, Palo Alto, Calif.... Also on June 11, 1961, the Myasthenia Gravis Foundation (155 East 23rd Street, New York City 10) will hold the semiannual meeting of its National Medical Advisory Board. All communications should be directed to Dr. Gilbert H. Glaser, Secretary of the Foundation's Advisory Board, Yale University School of Medicine, New Haven, Conn.

New Training Program in Neurochemistry As of July 1, 1961, a new program for the training of neurologists in neurochemistry will be initiated in the Division of Neurology at the University of Minnesota School of Medicine under the direction of Maynard M. Cohen. The program is supported by a grant from the National Institute of Neurological Diseases and Blindness. All inquiries should be addressed to Maynard M. Cohen, M.D., Professor, Division of Neurology, University of Minnesota Medical School, Minneapolis 14, Minn.

Symposium on the Sphingolipidoses Held in Brooklyn

On March 29 and 30, the Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, and the New York Downtown Medical Center held a two-day symposium on "The Sphingolipidoses and Allied Diseases." Bruno W. Volk, Director of the Isaac Albert Research Institute, organized the symposium. The participants made up a distinguished array of neurologists and scientists from American and European universities who presented studies on Tay-Sachs disease and other chronic disorders of the nervous system. The program was broad and multidisciplinary and included relevant studies in the biochemistry, histochemistry, neuropathology, electron microscopy, and genetics of the sphingolipidoses. The sessions terminated with a resume of studies of the emotional and psychologic effect on family living habits resulting from the occurrence of these conditions within the family group. Among the invited visitors from abroad were J. N. Cummings (London); Gunnar Brante (Eskilstuna, Sweden); G. W. Edgar (Amsterdam); S. Gatt (Jerusalem); and E. Klenk (Cologne, Germany).

U.S. Scientists Report on Soviet Child Care

Soviet progress in maternal and child care has been impressive since 1917. This is the concensus of 6 top American scientists who recently returned from a thirty-day exchange visit to the Soviet Union sponsored by the National Institute of Neurological Diseases and Blindness. The delegation observed that Soviet maternal and child care, while inferior in some ways to our best, assures every mother and her offspring better treatment than that received by many of America's indigent. They felt that availability of prenatal care in the Soviet might account for the current low infant mortality rate--1 in 25--as compared with the rate in 1917, which was 1 in 4. The scientists pointed out, however, that the Soviets do not use the standard international definitions of birth and prematurity. The delegation included Stewart Clifford, chairman, who is chief of newborn service at Children's Hospital, Boston, and head of infant care at the Boston Lying-In Hospital; Allan C. Barnes, chief of the Department of Gynecology and Obstetrics at Johns Hopkins; Katherine Bain, deputy chief, Children's Bureau, Washington, D. C.; Bernard G. Greenberg, professor of biostatistics and head of department, School of Public Health, University of North Carolina; Edith L. Potter, professor of pathology in the Department of Obstetrics and Gynecology, University of Chicago; and Fred S. Rosen, research fellow in medicine, Children's Hospital, Boston. A full report on the trip will be published later this year.

Research Foundation Offers Fellowships

The National Neurological Research Foundation, a voluntary organization in Washington, D. C. dedicated to the support of basic scientists conducting research on the nervous system, announces that it is

now accepting applications for its senior fellowship program. Fellowships carry annual stipends of $12,000 a year for five years. Fellowships may be activated through December 31, 1961. Fellowship awards are determined by the Foundation's scientific committee, comprising Raymond D. Adams, Edward M. Dempsey, Louis S. Goodman, Seymour S. Kety, Oliver Lowry, Horace W. Magoun, James L. O'Leary, and A. Earle Walker. Inquiries should be directed to the National Neurological Research Foundation, 3255 N Street, N. W., Washington 7, D. C.

Here and There Recent lecturers at the National Institutes of Health were John Szentagothai, Professor of Anatomy at the University of Pecs (Hungary), and Professor Giuseppe Moruzzi, Department Head of Physiology, University of Pisa. Professor Szentagothai lectured on cerebellar synaptology (April 11 and 12) and Professor Moruzzi on problems in the physiology of sleep (April 10).... A new muscular dystrophy clinic has been established at Duke University Medical Center, Durham, N. C., under Albert Heyman, Associate Professor of Medicine (Neurology), and Jerome S. Harris, Professor of Pediatrics. The Division of Neurology and the Department of Pediatrics are participating in the clinical program.... The centenary of the birth of Sir Henry Head will be celebrated at the London Hosptal on Thursday, August 31, 1961. Special lectures on the various aspects of Head's contribution to neurology will be given by Sir Esso Brane, Dr. Macdonald Critchley, and Drs. K. W. Cross and Ronald Henson. All neurologists from abroad who are in London are welcome to attend. Communications should be sent to R. A. Henson, M.D., F.R.C.P., Neurological Department, London Hospital, London E1.... The twenty-ninth Annual Meeting of the Harvey Cushing Society was held in the Hotel Del Prado, Mexico City, April 16 through 19, 1961.... The National Institute of Neurological Diseases and Blindness has recently produced a second film in a series of neurologic examination films, entitled "The Neurological Examination of the One Year Old." The film depicts procedures used in examining a child's development at 1 year of age, showing both the normal and abnormal responses. The new film was produced by Churchill-Wexler under the scientific direction of Dr. Richmond S. Paine, pediatric neurologist and Director of the Maternal and Infant Health Study at the Children's Hospital Medical Center in Boston. Prints of the film may be purchased for professional showings from Churchill-Wexler, 801 N. Seward Street, Los Angeles, or secured on a loan basis from Churchill-Wexler from NINDB, Bethesda 14, Md....

Briefs On May 8, Harry M. Zimmerman and A. Earle Walker will visit Japan to lecture before the neurosurgical group of the University of Kyoto.... AAN honorary corresponding member Professor Shigeo Okanaka has been awarded the Imperial prize of the Japan Academy of Sciences for his work on the autonomic nervous

system.... Matthew T. Moore has been elevated to full professor of neuropathology in the Graduate School of Medicine of the University of Pennsylvania.... Hans H. Reese is now in Cairo on a Fulbright.... J. D. Robertson, formerly electron microscopist of the Department of Anatomy of University College, London, has joined the neurochemical staff of Jordi Folch-Pi at the McLean Hospital (Waverly, Mass.).... David B. Clark, Associate Professor of Pediatric Neurology, Johns Hopkins Hospital, will open the 1961 Lecture Series of the Lynchburg Training School and Hospital with a lecture in clinical demonstrations of vascular injuries in childbirth (April 13 and 14) and a lecture on migraine in childhood (April 15).... Benjamin Pasamanick, Professor of Psychiatry at Ohio State University and Director of Research at the Columbus Psychiatric Institute, received the $500 Stratton award of the American Psycopathological Association for his study of the epidemiology of mental disorder.... Harry M. Zimmerman announces that Lucien J. Rubinstein of Dorothy Russell department at the London Hospital will join, as neuropathologist, his staff at the Montefiore Hospital as of June 1, 1961.

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References: 1. Finkel, M. J.: M. Times 86:1391, 1958. 2. Doshay, L. J., and Boshes, L.: Postgrad. Med. 27:602, 1960. 3. A. M. A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, J. B. Lippincott Company, 1960, p. 264.

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THERAPEUTIC INDEX

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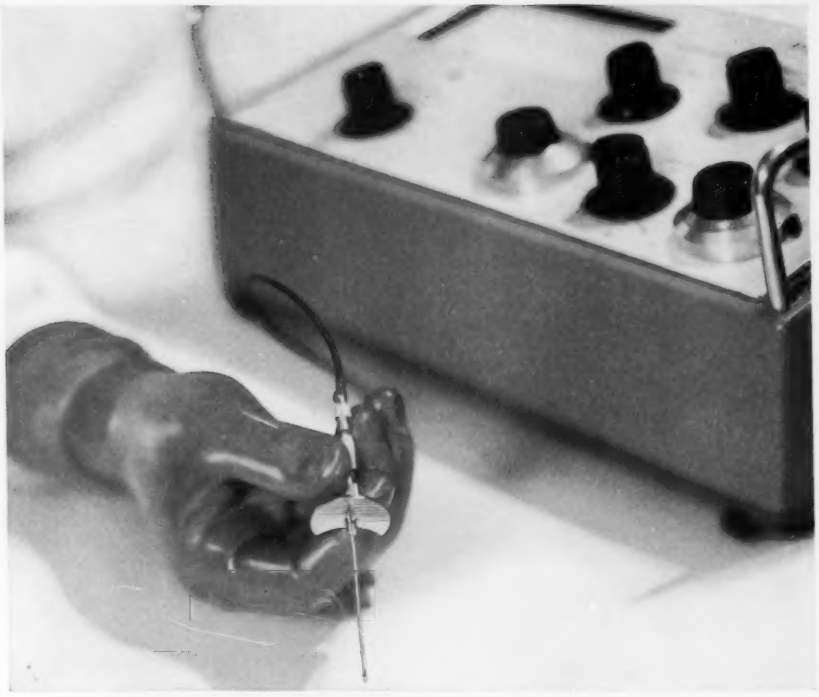

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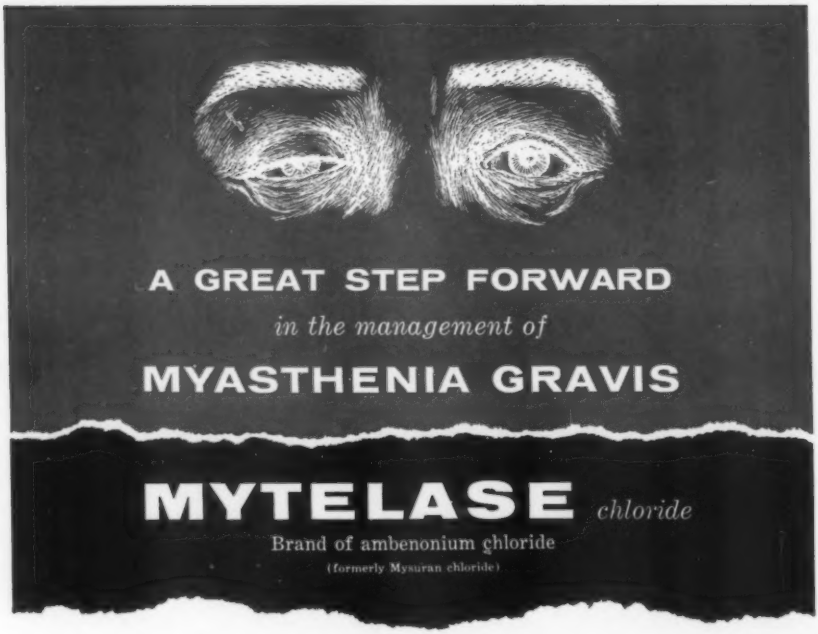

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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

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